Introduction: The transport of biomolecules like DNA, RNA and poly-peptides across protein membrane channels is of primary significance in a variety of areas. For example, gene expression in eukaryotic cells relies on the passage of mRNA through protein complexes connecting the cytoplasm with the cell nucleus. Although there has been a flurry of recent activity, both theoretical and experimental\textsuperscript{1,2} aimed at understanding this crucial process, many aspects remain unclear. By computing the potential of mean force (PMF) (which is defined as the free energy profile along a specified reaction coordinate), for the translocating biomolecule along the vertical axis of the protein pore, significant insight into the translocation process can be obtained. The details of the interaction of a pore with a translocating biomolecule within the confined geometries are critical in determining transport across a membrane. The interaction details can be captured best by fully atomistic simulations. The first fully atomistic simulations of the hemolysin pore have appeared very recently\textsuperscript{3}. They address however, only static properties — structural and electrostatic — and have not attempted to address the dynamic properties of the translocating DNA. The lack of more attempts at atomistic simulations of the translocation process is due in part to the fact that the computational requirements for simulations of systems of this size for the required timescales have hitherto not been possible. For example, the time scale for DNA translocation is of the order of tens of microseconds. Simulating such long timescales for large system sizes (275,000 atoms and upwards) is not possible with standard molecular dynamics approaches. To enhance our understanding there is a need now to adopt new algorithmic approaches in conjunction with new computing paradigms, as without significant advances at the algorithmic, computing and analysis levels, understanding problems of this nature will remain beyond the scope of computational scientists. SPICE aims to understand the vital process of translocation of biomolecules across protein pores, in ways that have not been possible until now, by using novel physical algorithms along with sophisticated grid infrastructure to effectively utilise the computational resources of a federated, trans-Atlantic Grid and to facilitate novel analysis techniques.

FIG. 1: Snapshot of a single stranded DNA beginning its translocation through the alpha-hemolysin protein pore which is embedded in a lipid membrane bilayer. Water molecules are not shown. Fig. (b) is a cartoon representation showing the seven fold symmetry of the hemolysin protein and the beta-barrel pore.
Scientific Methodology: An opportunity for a novel algorithmic advance is provided by a combination of Steered Molecular Dynamics (SMD) and Jarzynski’s Equation (JE). Although the combination of SMD and JE represents an important algorithmic development, utilizing it effectively for a problem of the size and complexity of translocation through nanopores using “regular” computing approaches poses significant if not insurmountable problems. The objective of SPICE is to overcome such barriers by the use of Grid computing—a computing approach that facilitates the coordinated utilization of a much larger set of resources for a single problem. Although this paper will focus on the advances arising from the use of Grid computing, we briefly outline the approach using SMD and JE. The application of an external force in a SMD simulation increases the timescale that can be simulated up to and beyond microseconds, whilst Jarzynski’s Equation provides a means of computing the equilibrium free-energy profile (FEP) in the presence of non-equilibrium forces. Thus, SMD simulations provide a natural setting to use Jarzynski’s equality, and hence the combined approach is referred to as the SMD-JE approach. Rather than a single detailed, long running simulation over physical timescales of a few microseconds (the typical time to solution for which will be months to years on one large supercomputer), SMD-JE permits a decomposition of the problem into a large number of simulations over a coarse grained physical timescale with limited loss of detail. Multiple SMD-JE non-equilibrium simulations of several million time-steps (the equivalent of several nanosecond equilibrium simulations) can be used to study processes at the microsecond timescale.

Using SMD-JE to compute $\Phi$: The first stage is to use “static” visualization (visualizations not coupled to running simulations) to understand the structural features of the pore. The need to understand the functional consequences of structure, as well as the desire for information on forces and dynamic responses, however, requires the coupling of simulations to the visualizations. These are referred to as interactive molecular dynamics (IMD) simulations. In interactive mode, the user sends data back to the simulation running on a remote supercomputer, via the visualizer, so that the simulation can compute the changes introduced by the user. Given the size of the model, in order that the simulation can compute forces quickly enough so as to provide the scientist with a genuine sense of interactivity typically requires performing simulations on 256 processors. IMD simulations are also extended to include haptic devices to get an estimate of force values as well as to determine suitable constraints to place.

IMD simulations also play another important role: in order to realistically benefit from the intrinsic ability provided by the SMD-JE approach to decompose an otherwise very substantial single computational problem into smaller problems of shorter duration, it is critical to find the values of the parameters that provide an “optimal PMF”. These parameters are the pulling velocity ($v$) and spring constant ($\kappa$) of the pulling atom to the SMD atoms. A rigorous analytic relationship between the combined statistical and systematic fluctuations of the PMF ($\Phi$) and the values of $v$ and $\kappa$ does not exist. Thus, there is a need to determine the parameter values which will minimize systematic and statistical errors such that, when used to compute the PMF of DNA translocating along the axis of the pore, they provide an optimal PMF, that is, a balance between systematic and statistical errors for a given computational cost. The qualitative understanding gained via IMD simulations helps in determining the initial range of parameters over which we will subsequently try to find the optimal value.

Once we have gathered sufficient insight from the interactive phase, we proceed to the batch phase, which has two sequential phases: in the first phase multiple simulations at different values of parameter space are performed the results of which are carefully analysed so as to determine the optimal parameters rigorously. In the second phase of batch runs, the complete, extended and accurate PMF is computed using the parameter set determined to be optimal.

Grid Infrastructure — Enabling Novel Simulations and Analysis Methods: We now discuss how the use of grid infrastructure facilitates the computation of the PMF. We use the capabilities developed by the RealityGrid project to render the SMD-JE approach amenable to an efficient solution on the Grid, by using
The ability provided by the Grid to easily launch, monitor and steer a large number of parallel simulations. It is wasteful to task farm a large number of HPC jobs to determine interesting parts of parameter space before analysis — the rationale for computational steering but task-farming many large scale simulations at a specific value of the parameter set after analysis on the scale required in SPICE requires using grid middleware and is both a challenge and an effective means of reducing the time to solution as well as the computational overhead. The feature to checkpoint and clone simulations provided by the RealityGrid infrastructure can also be used for verification and validation (V&V) tests without perturbing the original simulation and for exploring a particular configuration in greater detail. The RealityGrid steering framework — the architecture of which is outlined in Fig. 2a — has also enabled us to easily introduce new analysis and intuition building approaches; in particular, here we make use of haptic devices within the framework for the first time. In particular, in this paper we will focus on the use of the advanced network called UKLight and how it facilitates the interactive component of the above mentioned scientific methodology.

We use the infrastructure consisting of a distributed set of supercomputers — on both the UK National Grid Service as well as the US TeraGrid — for our simulations, plus a dedicated visualization resource (SGI Prism) at UCL. The visualization engine is connected to the HPC resources in the UK and to the TeraGrid resources via Starlight in Chicago using a dedicated optically switched network called UK Light, which ensures a dedicated low latency, high speed network connection between the simulation and visualization. The haptic is connected to the SGI Prism through multi-Gigabit LAN. The resources used and shown in Fig. 2a are grid enabled in the sense that Globus toolkit version 2 (GT2) is used. The ability to distribute over a federated grid enables greater resource utilization as well as a single uniform interface. Hiding the heterogeneity of different resources is a major convenience for the scientist who no longer needs to worry about site-specific issues.

**Haptic Device:** The Phantom Omni device (Sensable) is a force-feedback haptic device with 6 degrees of freedom which plays an important role in the IMD stage of the analysis and its use has been integrated into the RealityGrid framework. The device is connected to a controlling computer via an IEEE-1394 (‘firewire’) link. The VMD visualisation package requires an additional software package, VRPN, which provides a network transparent interface to the haptic device based on UDP communications. A separate computer running Windows XP was employed to run a dedicated VRPN server. Because of the restriction on dual-homing the Prism, a dedicated private network was created, using a direct connection between the VRPN server and a spare GigE interface on the Prism.

**UKLight: A brief Introduction:** Many research fields increasingly require data communications between remote sites in the multi-Gigabit per second range. Examples include scientific data transport, Computational Science, Visualization, Environmental Modeling and Medical applications requiring high volume remote imaging. Often these applications require connections between a well-defined and stable set of endpoints, which must be sustained for hours or days, and/or have stringent constraints on the levels of service required from the network. Such characteristics are both difficult and costly to meet with traditional IP-based (packet-switched) networking, and these needs may be best addressed through the use of switched optical networks. In recognition of this, several leading national network organizations have created an international experimental testbed to pilot this new paradigm of networking. These include as founding partners StarLight in the USA, NetherLight in the Netherlands and the Canadian academic network CANARI. With the construction of UKLight, the UK joins the Global Lambda Infrastructure Facility (GLIF). Figure 3 shows existing infrastructure of the GLIF, which provides an idea of the connection capability to remote collaborators. UKLight is managed by UKERNA on behalf of the UK research and education community.

The UKLight Network: UKLight comprises a hub in London, located at the University of London Computing Centre, with 10 Gbit/s connections to StarLight in Chicago and NetherLight in Amsterdam. These links can be multiplexed to provide access to low-level switched circuits (e.g. Gigabit-Ethernet circuits) to collaborators in the rest of the world (provided they are themselves able to access the global testbed). Access to UKLight from institutions within the UK is provided by an extended national development network alongside the SuperJANET.
FIG. 4: The diagram shows the international components of UKLight together with phases 1 and 2 of the extensions to the JANET development network through which projects gain access to the facility.

production network. In the future there may also be a dark fibre testbed within the UK connecting institutes participating in optical component demonstrations.

UKLight, including the national R&D network extension, is a facility which is provided to enable and advance all areas of research, development and other collaborative applications in all fields. The principal criterion for use is that the work to be undertaken should genuinely need dedicated or very high bandwidth switched connections, and that it would not be simply provided for by the existing IP based production network. Data intensive applications projects can develop new ways of working based upon the ability to transport and manage data sets using scheduled bandwidth on demand services. Applications requiring dependable quality of service across long distances can be developed, including bandwidth-intensive remote visualization uses. Network researchers will be able to develop both the control models and protocols needed to build scalable switched optical networks\[12]. In addition to RealityGrid scientists using established persistent connections to the TeraGrid in the USA for visualization experiments as part of the SPICE project as well as in LB3D studies\[13], some other projects utilizing the facilities are the Particle Physics Community (a 1 Gbit/s Ethernet circuits between the UK and the FermiLab Computer Centre in Chicago) and the Radio Astronomy Community (using circuits to the Netherlands to extend the capability of their very long baseline interferometry radio telescope program). The eDiamond project also plans the use of Gigabit circuits to enable remote radiography stations to transport and view large mammography images.

**SPICE and UKLight:** SPICE is a project that builds critically on real-time visualization and interactivity. As discussed in the Scientific Methodology section, IMD simulations play an important role in both advancing the scientist’s understanding of dynamical responses to controlled perturbations as well as in narrowing the search space of optimal PMF parameters. SPICE represents just one instance from a class of many biomolecular simulations that requires a visual front end to provide interactivity — as opposed to the simpler case of just changing parameter values — for simulations running on high-end resources. As a consequence of the large size and complexity of the systems of interest, a substantial fraction of the high end compute resources are required in order to simulate the systems fast enough so as to provide real-time interactivity. Similarly, high end visualization resources are often entirely dedicated to the task at hand, in order to provide sufficiently fast rendering and other visualization requirements so as to avoid hindering interactivity. It is important to note that the communication between the visualizer and the simulations is bi-directional. When using 256 processors (or more) of an expensive high-end supercomputer it is not acceptable that the simulation be stalled, or even slowed down due to unreliable communication between the simulation and the visualization; thus a general purpose network is not acceptable. Advanced (optically switched) networks that ensure schedulable capacity for high rate/high volume communications, as well as bounded quality of service (QoS) in terms of packet latency, jitter and packet loss are critical for such interactive scenarios.

In the most generic and flexible setup, the user should be free from being colocated with the visualization resource — just as the user is no longer constrained to be located at the console of the computational resource. Once again for this is to be realized there must exist well defined network QoS. We are planning experiments to test the effect of QoS characteristics (bandwidth, latency and jitter) on visual applications by comparing their behaviour over UKLight and production networks.

Our application produces at least 1Gigabyte of data for every nanosecond of simulated physical time. In this first phase of batch runs used to compute the optimal PMD parameter values, we have generated and analysed 50GB of data. Approximately one further terabyte of data will be generated and analysed in the computation of the extended and accurate PMF. Although this data will not be generated over a period of a couple of days as was in the TeraGyroid project, but more likely over a month, the use of UKLight as opposed
to regular networks will make the transfer of such volumes of data more efficient. In the absence of a grid-wide network file service, with distributed visualization services it is often the case that the same dataset needs to be replicated in more than one location. Thus, although the net output per nanosecond is about 1 GB/second, due to the need to replicate datasets over different resources — which in turn depends upon the infrastructure used — the aggregate data transfer can be many multiples of the amount generated. So although SPICE primarily needs to use UKLight for well defined network QoS, the high bandwidth provided by UKLight is important and provides valuable flexibility in cloning simulations for V&V and further analysis.

**Effect of UKLight on IMD Performance:** NAMD is an open source molecular dynamics code that supports computational steering and IMD using the associated package VMD. Of particular significance to the SPICE project is the ability to use VMD to apply a force to the DNA strand inside the pore and study its effect. The force maybe applied to a single atom, a certain residue, or the entire molecule. After the choice of atoms to which to apply the force is made, VMD sends information about the forces (magnitude, direction and choice of atoms) applied to the NAMD simulation. On receiving this information, the simulation incorporates the forces transmitted into the calculation at the next step and then sends updated coordinate and velocity information back to the visualizer. The interval at which communication between NAMD and VMD takes place is a user controlled variable; for the most realistic effect the communication should ideally be set to occur every simulation timestep, especially if a haptic force feedback device is to be used.

We will return to this point later in the last section, but it is worth mentioning briefly now that software often needs to be customized and tuned to take advantage of advanced network features and that although desirable, it is rather difficult to exploit network features for an application straight out of the box. For example, irrespective of whether VMD is used or not, NAMD undergoes a slowdown whenever it is set to be used in IMD mode.

This is probably because at the beginning of a timestep, when expecting IMD data, NAMD looks for any data that may have arrived from VMD since the last time it checked; if any arrives it attempts to incorporate this data into the calculation for the current timestep. As I/O is done by a single-thread there is some stalling as a consequence.

At the time of writing (early August 2005) the only sufficiently large multiprocessor machine within the UK that is connected to UKLight and to which we have access is the SGI Onyx3800 machine (Green) at CSAR. Consequently we carried out performance tests using 64 processors on Green and the visualization machine at UCL (Prism). Note that ideally 256 processors of Green would be used for interactive studies but in order to use 256 processors in a well defined time interval typically requires advanced reservation. For NAMD running on 64 processors of Green, we find that simply switching from “IMDon no” to “IMDon yes” results in a slowdown of about 2%, i.e. wallclock time increases from 0.68 seconds/timestep to 0.70 seconds/timestep. Next we actually connect a VMD session to the running simulation (as opposed to just modifying the input configuration but not connecting VMD). First we connect VMD running on the Prism to the simulation running on Green. In this configuration all traffic flows over UKLight. We find that the mean time per timestep is 0.76 seconds, which is in itself approximately 10(12%) slower than for NAMD used without VMD but with the “IMDon” flag set to yes(no). However, when the same scenario is repeated running VMD on a desktop machine the time per timestep is approximately 1.05 seconds: the desktop machine is connected to the production network using only a Gigabit ethernet interface.

It is fair to assume that the performance of VMD is the same on both machines; it is also a correct approximation that the difference in the two machines does not introduce any discrepancies. Admittedly the desktop machine (non-UKLight) running VMD is not as “heavy duty” as the Prism, but a check using “top” confirms that the observed performance difference is not related to the load that VMD is placing on the machines.

Thus the critical component that is responsible for the performance hit when using the IMD feature is the comparatively large fluctuations in the round trip time (RTT), available bandwidth and packet loss/reordering encountered on a regular network. These issues do not occur when UKLight is used.

Not surprisingly, when using a machine on the other side of the Atlantic the RTT does not change much between the two networks as the dominant component of the RTT is the time taken for the signal to travel the several thousands of kilometres. We anticipate that loss/reordering and variability continue to play a role, and that there will still be an advantage to using UKLight over production network; any advantage though will probably be more limited as the dominant component of slowdown is not network-induced latency anymore. We need to perform more experiments however, to better understand the effect of network characteristics on our applications and to begin to quantify that advantages of UKLight. There is also the issue of dependence on the number of processors used which alters communication to computation ratio in the execution of the program. We have not so far studied such effects explicitly, partly because of the requirement for advanced reservation as alluded to earlier. We plan to perform these in the near future.

**Discussion:** As this is a paper documenting our experience, we conclude by discussing some of the other experiences and issues we have encountered in attempting to make use of optically switched networks.

**Getting connected:** One of the major problems when connecting a production machine to a dedicated network for research purposes is security: the production side of the machine is supposedly going to be behind one or more firewalls that control access to this resource from the outside of the campus but adding a new connection could result in potentially bypassing these firewalls and thus jeopardizing the security of the whole network. Obviously local arrangements are going to differ based on the local security policies but in general what tends to be done is to tighten security on the machine, reduce the number of ports (i.e. services) available, make sure that the machine itself is not routing traffic between the campus network and the research network and limit the number of networks that are reachable on each physical network connection. Normal security measures like firewalls cannot usually be deployed on the research side mainly for two reasons: firstly, these research links provide high speed links (1/10 Gbit/sec) and a hardware firewall would be expensive; the principal problem, however, is that it is really difficult to define rule-sets to apply to these firewalls in the context of Grid applications. It
is important to note that it is generally not possible to have a production machine connected only to dedicated networks like UKLight. Production machines serve a much wider community of users and this service much be maintained hence, disconnecting from production networks is not an option. Also these production machines need to be accessible from clients that are not themselves connected to the dedicated networks. Therefore the only option is to have dual homed systems — machines that have two IP addresses on two different networks. Unfortunately, dual homed systems present a different set of problems. For example, it was not possible initially to use Gridftp as a third party data transfer mechanism between a machine that was on the dedicated network from a machine that wasn’t. In general retaining control over how traffic flows between two points in the above mentioned scenario remains very complicated (and sometimes impossible), especially given an opaque layer of application software and middleware between the end user and the network. GridFTP now enables such transfers but not with significant new versions and subtle configurations.

Software architecture issues: HPC parallel codes are seldom designed to support run-time, interactive communications with remote resources. When implemented, remote communications code is often adapted from code responsible for managing local (disk) IO. Although adequate, such an approach fails to anticipate the differing characteristics of disk and network subsystems. This can yield sub-optimal results which may result in large execution time-penalties when large volumes of data must be transferred. As a consequence of Amdahl’s law, to maximise parallel efficiency of NAMD, the time spent in network communications should be minimised. Inspection of the NAMD source code shows, that, when coupled with VMD, NAMD (here we are referring to the version of NAMD which uses system MPI libraries for inter-process communication) performs all communications serially: MPI processes send data to the rank 0 process and then block until rank 0 has successfully sent all data to the destination resource. From observation of network bandwidth usage, it is apparent that this design is unable to sustain a transmission rate which taxes the network capacity. Consequently, we observe that in order to realise significant usage of the bandwidth made available via UKLight, it would be necessary to redesign the IO system within NAMD. We believe that this will be a very common situation when using out-of-the-box parallel codes that have not been designed for novel network features. In contrast, GridFTP[6] a program designed to optimise network bandwidth use, adopts a multi-threaded, multi-channel design with parameters which may be tuned for a specific network configuration.

Delocalizing the haptic device from the visualizer: We propose to examine the performance of haptic control of VMD in the regime in which the ANL visualisation server is used in conjunction with a haptic server located in the UK. We will compare the ‘ease of use’ of haptic control of VMD between UKLight and production network links. (We define ’ease of use’ as the probability with which a user can expect to correctly perform of a set of haptic operations.) It has been reported elsewhere[10] that a haptic feedback latency of 200ms represents a threshold at which the ease of use of the device is significantly impaired. Because this limit is above the RTTs observed on both UKLight and production network transatlantic (UCL-NCSA) network paths (and since RTTs on both paths are similar) it is anticipated that any comparative impairment of haptic operation will arise when using the production network and will be a consequence of packet-loss and the jitter.

Conclusion: In conclusion, we have discussed the background and the scientific motivation of the SPICE project and how it utilizes grid computing capabilities — in particular advanced networks like UKLight — to achieve its scientific goals. The results of our simple yet significant performance tests show the advantages that the use of advanced networks like UKLight have on performance when using interactive simulations on expensive HPC resources. In the near future, we plan simple proof-of-concept experiments that will test new scenarios for implicit simulations that would not be possible without the use of advanced networks. It is worth noting that the grid computing infrastructure used here for computing free energies by SMD-JE can be easily extended to compute free energies using different approaches (e.g thermodynamic integration)[20]. This opens up our approach to many different problems in computational biology, e.g., drug design, cell signaling, where the computation of free energy is critical. Equally important, exactly the same approach used here can be adopted to attempt larger and even more challenging problems in computational biology as our approach is inherently scalable.

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17 http://www.uklight.ac.uk


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