

Phylogenetics

DPRml: distributed phylogeny reconstruction by maximum likelihoodT. M. Keane¹, T. J. Naughton^{1,*}, S. A. A. Travers², J. O. McInerney² and G. P. McCormack²¹Department of Computer Science and ²Department of Biology, National University of Ireland, Maynooth, Ireland

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ABSTRACT

Motivation: In recent years there has been increased interest in producing large and accurate phylogenetic trees using statistical approaches. However for a large number of taxa, it is not feasible to construct large and accurate trees using only a single processor. A number of specialized parallel programs have been produced in an attempt to address the huge computational requirements of maximum likelihood. We express a number of concerns about the current set of parallel phylogenetic programs which are currently severely limiting the widespread availability and use of parallel computing in maximum likelihood-based phylogenetic analysis.

Results: We have identified the suitability of phylogenetic analysis to large-scale heterogeneous distributed computing. We have completed a distributed and fully cross-platform phylogenetic tree building program called distributed phylogeny reconstruction by maximum likelihood. It uses an already proven maximum likelihood-based tree building algorithm and a popular phylogenetic analysis library for all its likelihood calculations. It offers one of the most extensive sets of DNA substitution models currently available. We are the first, to our knowledge, to report the completion of a distributed phylogenetic tree building program that can achieve near-linear speedup while only using the idle clock cycles of machines. For those in an academic or corporate environment with hundreds of idle desktop machines, we have shown how distributed computing can deliver a 'free' ML supercomputer.

Availability: The software (and user manual) is publicly available under the terms of the GNU general public licence from the system webpage at <http://www.cs.may.ie/distributed>

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1 INTRODUCTION

One of the great challenges of molecular biology is the completion of the tree of life. The massive accumulation of genomic data has led to increased interest in the production of large and accurate phylogenetic trees. However the decision problem associated with searching for the best tree from a set of taxa is NP-hard (Bodlaender *et al.*, 1992). Therefore it is not feasible to perform an exhaustive search of the tree space for trees of a non-trivial size. Maximum likelihood (ML) evaluation has been widely acknowledged as one of the

most accurate techniques for reconstructing phylogenies. Felsenstein (1981) first brought this framework to nucleotide-based phylogenetic inference. Numerous computer studies (Huelsenbeck and Hillis, 1993; Kuhner and Felsenstein, 1994; Huelsenbeck, 1995; Rosenberg and Kumar, 2001; Ranwez and Gascuel, 2002) have shown ML programs can recover the correct tree from simulated data sets more frequently than other methods. In a recent study timing the evolution of the HIV-1 virus (Korber *et al.*, 2000), it was demonstrated that ML techniques can be effective in solving important biological problems.

Currently the most successful heuristic approach for building phylogenetic trees is to employ a hill-climbing algorithm combined with ML evaluation. Each taxon is added to the tree in a stepwise manner and topological rearrangements are subsequently performed on the best tree, in an effort to avoid local minima in the search space. The most computationally intensive aspect of this approach is that each candidate tree that is generated must have its branch lengths optimized and likelihood calculated. Some of the most popular tree building programs (Felsenstein, 1989; Rogers and Swofford, 1998) are based on this method. Despite considerable improvements in runtimes (Olsen *et al.*, 1994; Guindon and Gascuel, 2003) the single factor that is currently limiting the widespread use of ML techniques in phylogenetic analysis is the huge computational requirements (Hershkovitz and Leipe, 1998). A number of other authors (Stewart *et al.*, 2001; Schmidt *et al.*, 2002; Stamatakis and Ludwig, 2003) have concluded that the major limitation with each of these programs is that they are limited to operating on a single processor, which means that it is not feasible to build large phylogenetic trees using these programs.

In an effort to construct large and accurate phylogenetic trees while still keeping overall processing times reasonable, a number of researchers have developed parallel ML programs that utilize the stepwise insertion approach (Stewart *et al.*, 2001; Stamatakis and Ludwig, 2003). One of these programs (Stamatakis and Ludwig, 2003) also employs some simple distance-based heuristics to try to reduce the number of generated trees. These programs have been successful in speeding up phylogenetic computations but the overriding problem with these programs is that specialized parallel hardware and software is often required. For most researchers, this can make these programs either prohibitively expensive or simply too complicated to set up. Furthermore these programs are often implemented in a platform-specific language which imposes a restrictive limit on

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the numbers and types of machines that can be used in a parallel computation. It should also be noted that some of these earlier parallel programs only allowed the user to choose from a very limited number of DNA substitution models, which often leads to a poor model fit resulting in suboptimal trees. Therefore, in our opinion, the three most essential requirements of any generally usable parallel tree building program must be that the program should not require any sort of specialized or expensive parallel hardware or software, should only require the most basic technical abilities to set up and use, and should allow the user to choose from an extensive list of molecular evolution models. Currently there is no parallel phylogenetic tree building program that fulfills all of these requirements.

We have identified the suitability of phylogenetic analysis to large-scale heterogeneous distributed computing and have developed a fully cross-platform distributed application, distributed phylogeny reconstruction by maximum likelihood (DPRml), which we believe to be one of the most general and powerful likelihood-based phylogenetic tree building programs currently available. DPRml is, to our knowledge, the first distributed phylogenetic tree building program to satisfy each of the three requirements outlined above. The generality of our program is demonstrated by the fact that DPRml, written in Java, can run on virtually any architecture and operating system simultaneously while only using the spare clock cycles of donor machines. No specialized computer hardware is required, and no expense is incurred if idle computing resources are harnessed. This would not be as straightforward for a distributed application written in a native language because the application would have to be compiled for each particular architecture and operating system. We have demonstrated the ease of use and platform heterogeneity of DPRml with experiments that utilize the spare computing resources of several different architectures and operating systems simultaneously. The user has a very straightforward configuration file with which to tailor the computation and can choose from one of the most extensive ranges of DNA substitution models currently available. Our performance analysis demonstrates how effective DPRml can be for speeding up the process of constructing large phylogenetic trees. DPRml implements an already proven tree building algorithm (Olsen *et al.*, 1994; Stewart *et al.*, 2001) and uses the popular Phylogenetic Analysis Library (PAL) v1.4 (Drummond and Strimmer, 2001) for all its likelihood calculations.

DPRml is just one application of large-scale distributed computing. Our intention with this paper is to highlight the general applicability of this computing paradigm to certain bioinformatics computations. By a detailed presentation of this specific example we wish to highlight the hallmarks of the paradigm which are ease-of-use, flexibility, affordability and efficiency.

2 DISTRIBUTED COMPUTING AND PHYLOGENETIC ANALYSIS

In recent years, the area of distributed computing has emerged as a viable alternative to specialized parallel computing. By harnessing the spare clock cycles of idle machines (Buyya, 1999), it is possible to emulate the computing power offered by a specialized parallel machine at a fraction of the cost. Several successful systems have been developed on this basis, e.g. Seti@Home (Korpela *et al.*, 2001), Folding@Home (Larson *et al.*, 2004), Condor (Thain *et al.*, 2003) and Models@Home (Kreiger and Vriend, 2002). The type of

applications that are generally considered to be suited to distributed computing have the capability to fully exploit 'coarse-grained parallelism,' meaning that it should be possible to partition the application into independent tasks or processes that can be computed concurrently. Typically these types of problems must display a high 'compute-to-data' ratio to make it worthwhile sending the data over a network rather than computing locally.

The process of constructing large phylogenetic trees using ML analysis generates thousands of candidate trees that must have their branch lengths optimized and likelihood calculated. These two processes can be done completely independently for each tree and the set of trees generated at each stage can be represented, stored, and transferred compactly using only a few Kbytes. Therefore the small size of the data involved coupled with the long computation times of ML analysis make this problem ideal for a large-scale distributed computing implementation.

2.1 DPRml algorithm

We have taken the hill-climbing algorithm used by parallel fastDNAmI (Stewart *et al.*, 2001) and have implemented a platform-independent, distributed and much more generalized version of the program. The algorithm implemented by DPRml is outlined in Figure 1. The parameters m and v are contained in the parameter file. Step 1 of the algorithm is a localized version of the overall algorithm outlined in steps 2–7. A single donor machine builds an initial tree for m minutes (default value is 30 min) as it is more efficient to build this initial tree on a single donor machine than to distribute this part of the computation. At each stage of the algorithm, the set of generated trees is split into equal size groups and issued to clients on a first come, first served basis. The inputs to the application are a MODELTEST (Posada and Crandall, 1998) output file, a FASTA sequence file (DNA or RNA) and an input parameter file. The outputs of the program are a Nexus format tree file, a Newick format tree file, a PAL tree object file, a human readable tree (text file) and the likelihood of the final tree. We have provided a remote interface to the system that makes it possible to monitor the progress of the application in real-time as it builds the phylogenetic tree. The program supports all of the DNA substitution models that MODELTEST v3.06 provides. The input parameter file lets the user set various runtime options for the computation such as the maximum number of vertices that rearrangements can span, whether to keep a copy of the best tree from every stage or just the best tree from the previous stage, whether to add the taxa in a randomly generated order or input order, and whether to optimize the branch lengths of every tree that is generated or just optimize the final tree. If there was a catastrophic event (e.g. a system wide power failure), it is possible for the program to continue building the tree from where it left off. Log files make it possible to fully examine and track the entire tree building process.

2.2 Implementation

DPRml is implemented entirely in Java, meaning that the program is completely platform-and-network-independent. DPRml is just one of the applications that can run on our general purpose distributed computing platform, loosely based on the design of the Java distributed computing library (JDCL) (Fritsche *et al.*, 2001; Keane *et al.*, 2003). In our deployment of DPRml, we have our client software running in a number of computing laboratories, consisting of approximately 200 desktop PCs of various modest specifications (Pentium IIs up

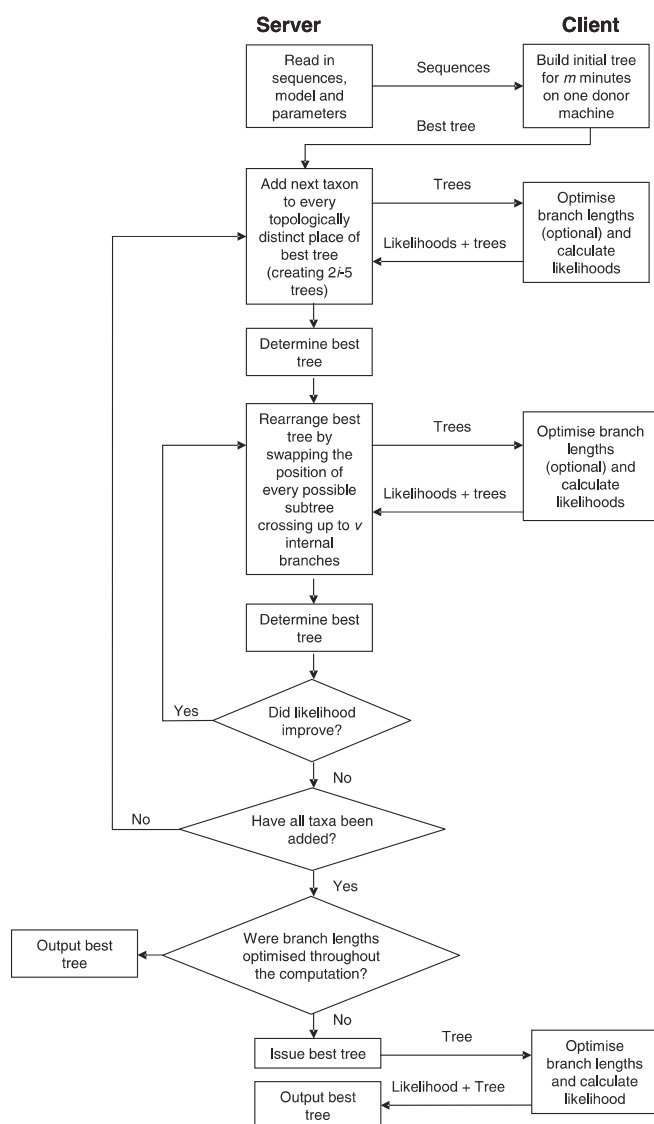


Fig. 1. Tree building algorithm implemented by DPRml.

to Pentium IVs running assorted versions of Windows and Linux OSs). To minimize disruption to users, we run the client as a low-priority background service that only uses the idle clock cycles of the machines. To illustrate the portability of our system, we have also installed our client on every node of an IBM Linux cluster (32 Dual PIII 1 GHz nodes with between 256 and 768 MB memory per node) with the desktops and cluster nodes connecting to a single server.

3 PERFORMANCE ANALYSIS

A number of standard measures have emerged in parallel computing for measuring the performance of parallel programs. Running time measures the amount of time from when a parallel program is started to when the program produces the final result of the computation. Speedup s is the ratio between the running times using one processor and multiple processors. It measures the performance improvement

Table 1. Runtime comparison of DPRml and FastDNAml for the three data sets (50, 101 and 150 taxa). All times are in minutes

	50 Taxa	101 Taxa	150 Taxa
DPRml	1386	57 373	123 484
FastDNAml	240	8726	14 685

gained through parallelization and is calculated from

$$s(n) = \frac{t(1)}{t(n)}, \quad (1)$$

where $t(1)$ is the running time of the program using a single processor, and $t(n)$ is the running time of the program using n processors. The maximum theoretical speedup occurs when there is an n times speedup achieved using n processors. The ideal speedup curve is rarely achieved because parallelism entails a certain amount of communication and management overhead. It should also be noted that the maximum speedup achievable depends greatly on the degree of parallelism in a particular algorithm (Amdahl, 1967). Scalability is the ability to maintain performance levels as the workload increases by incrementally adding more system capacity (adding more processors and/or computations running simultaneously).

We performed a full set of performance tests using the data set that was used to benchmark parallel fastDNAml (Stewart *et al.*, 2001). This data set consists of three individual sets of taxa consisting of 50 taxa, 101 taxa, and 150 taxa that are 1858 (50 and 101 taxa) and 1269 (150 taxa) nucleotide positions in length. In our tests, we used the HKY (Hasegawa *et al.*, 1985) DNA substitution model with the same three Ts/Tv ratio parameters as were used by parallel fastDNAml. We examined several trees constructed by DPRml using this data set and found that there were only minor differences due to the differing randomization of the taxa addition order. Several of the trees produced are available from the system webpage. For all of our performance tests, we ran a version of the program that adds the taxa to the tree in the same order each time (so that the scaling behavior of the program could be clearly understood) and the program was configured to optimize the branch lengths of every tree generated. The maximum number of vertices that rearrangements could cross was set to five.

We compared the single-processor performance of DPRml and fastDNAml (Olsen *et al.*, 1994) using the three data sets. The results of these tests are shown in Table 1. Although DPRml performs approximately seven times slower than fastDNAml, DPRml's performance reduction is overcome by its greater cross-platform compatibility.

3.1 Single problem speedup analysis

To analyse the speedup that can be gained by running DPRml, we ran a single instance of DPRml on the distributed system with differing numbers of clients and noted the total running time in each case. For these particular tests, the set of clients consisted of two university computing laboratories with a total of 60 desktop PCs (each machine was a Pentium IV 2.4 GHz with 512 Mbytes of memory running either Windows 2000 or Redhat Linux 7.0). Our server resided on a Pentium III 600 MHz with 256 Mbytes of memory running Debian

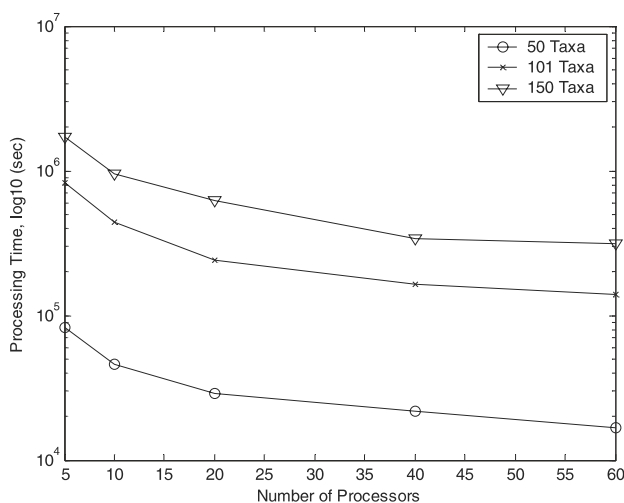


Fig. 2. Decrease in computation time with an increase in the number of processors over each of the three data sets (50, 101 and 150 taxa). The average over two runs for each data set is shown.

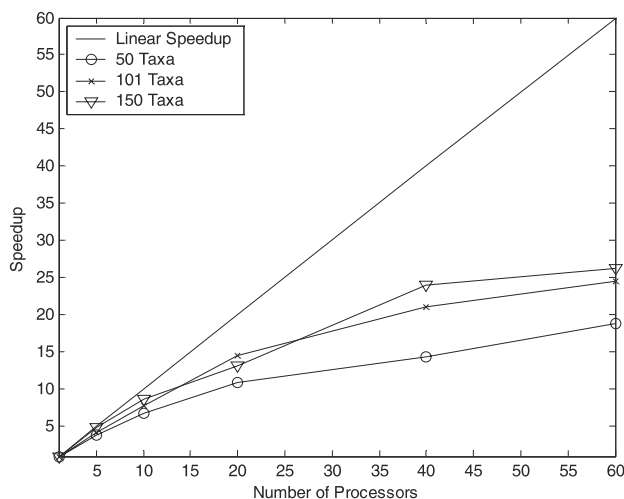


Fig. 3. Speedup achieved over each of the three data sets (50, 101 and 150 taxa). The average over two runs for each data set is shown. Linear speedup is the theoretical maximum for parallel algorithms.

Linux with a 10 Mbit/s connection to the laboratories. We had our client installed as a low-priority background service and the PCs were in use, and were being rebooted between operating systems during teaching hours. The graphs show the corresponding mean running time decrease (Fig. 2) and speedup gained (Fig. 3) over two runs for each point on the graphs. The main factor limiting the scalability of the program is the synchronization barrier created by the staged nature of the algorithm. If any of the donor machines are unexpectedly switched off, DPRml must wait for the distributed system to detect this and redistribute the data to another donor machine before it can proceed to the next stage of the algorithm. Figure 3 shows that DPRml scales extremely well, with the speedup increasing with an increase in data set size. This is consistent with the findings of a special purpose parallel phylogenetic program (Stewart *et al.*, 2001). For this particular data set, it is expected that the speedup gains

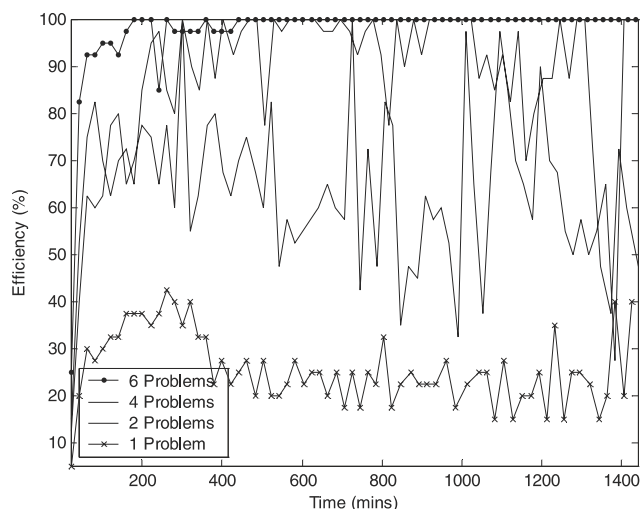


Fig. 4. Efficiency of the system over a period of 24 h for varying numbers of DPRml computations running in the system.

Table 2. Average tree size after 24 h for varying numbers of DPRml problems running simultaneously in the distributed system

# Problems	1	2	4	6
Tree size	72	58	54	49

should plateau at approximately 150 processors because at this point the number of processors would equal the number of trees being generated at many of the stages. This would also be the case for any other parallel tree building program.

3.2 Multiple problem efficiency analysis

One way to maintain consistently high efficiency (utilization of donor machines) in the distributed system is to run several DPRml computations simultaneously. Ideally, each computation would be at a different stage in the tree building algorithm and therefore should result in consistently higher overall efficiency. Multiple DPRml computations can be submitted to the server, which allows users to always make optimal use of the available donor machines. We wanted to investigate fully how to optimize the efficiency of the distributed system by running differing numbers of DPRml computations simultaneously. We were also interested in the extent to which an increasing number of DPRml computations running simultaneously would affect the rate at which the phylogenetic trees are built. To investigate these two related issues, we used one of the data sets that was used to test parallel fastDNaml (Stewart *et al.*, 2001), consisting of 101 taxa (1858 nucleotides per taxa), and we ran varying numbers of DPRml computations on the system while keeping the number of donor machines fixed. The set of clients consisted of a university computing laboratory with a total of 40 desktop PCs (each machine was a Pentium III 600 MHz with 128 Mbytes of memory running Windows NT). By examining the distributed system log files, we completed a graph (Fig. 4) showing the efficiency of the system over a period of 24 h for each set of problems. We also noted the average size of the trees built (Table 2) at the end of each 24-h period.

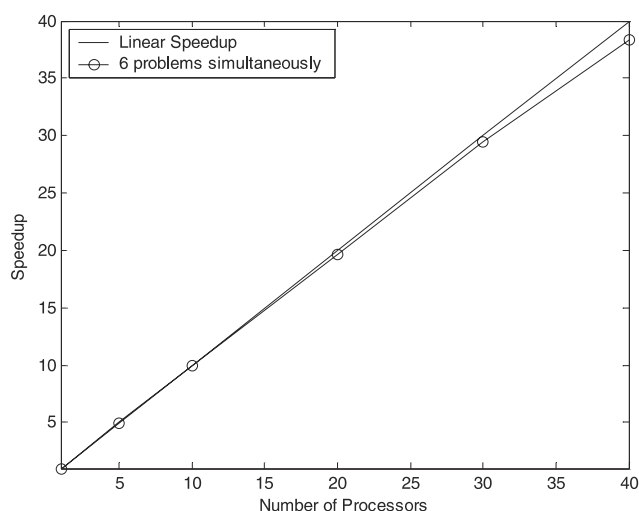


Fig. 5. Speedup achieved over 50 taxa data sets with six problems running simultaneously. Linear speedup is the theoretical maximum for parallel algorithms.

Figure 4 shows that efficiency is greatly increased when the number of tree building computations running simultaneously in the system is increased. Table 2 is quite interesting as it shows that by increasing the number of tree building computations from one to six only reduced the average tree size by 31%. For this particular data set and set of donor machines, six tree building computations is sufficient to get almost 100% efficiency from the system. To further investigate the effect on speedup of running multiple DPRml computations in the distributed system, we completed a speedup graph (Fig. 5) based on the running time of six simultaneous DPRml computations. For this test, we used one of the data sets that was used to test parallel fastDNAmI (Stewart *et al.*, 2001), consisting of 50 taxa (1858 nucleotides per taxa), and ran six simultaneous computations with varying numbers of clients. As expected, Figure 5 demonstrates that DPRml achieves near-linear speedup when speedup is measured with multiple DPRml computations running simultaneously.

The above results fit well with the expected usage of the program. As the algorithm outlined in Section 2 is heuristic, it is possible to become trapped in a local optimum, rather than a global one. Typically a researcher would repeat the entire tree building process with several different randomizations of the taxa addition order and then compare the best of the resulting trees to determine a consensus tree (Jermin *et al.*, 1997). As has been noted by parallel computing authors (Amdahl, 1967), it is quite rare and difficult for a parallel or distributed system to achieve 100% efficiency. We are the first, to our knowledge, to report the completion of a distributed phylogenetic tree building program that can achieve near-linear speedup and almost 100% system efficiency while only using the idle clock cycles of standard desktop machines.

4 DISCUSSION

DPRml is an easy-to-use practical application that can harness the idle computing resources of any research institute to construct large phylogenetic trees using ML. The real significance of DPRml lies in the fact that it gives a researcher, who may not have access to (or the technical skills necessary to access) a dedicated parallel machine,

the ability to build large and accurate phylogenetic trees. Unlike other parallel phylogenetic programs, no specialist parallel computing knowledge is required to set up and run DPRml. The program offers an extensive list of DNA substitution models that allows users to pick the substitution model that better reflect their data set. We have shown how effective DPRml can be for speeding up phylogenetic computations by performing a full performance analysis. The final outputs of the program are in standard formats that allow the user to perform further manipulation and analysis of results using other phylogenetic packages.

This first release of DPRml uses PAL v1.4 (Drummond and Strimmer, 2001) for all of its optimization and likelihood calculations. As new features and algorithmic improvements appear in later versions of PAL (Goode *et al.*, 2004), we will release updated versions of DPRml on our webpage to take advantage of the improvements. In future versions of DPRml we plan to improve performance by focusing our investigations on algorithmic improvements and plan to add features such as bootstrap analysis and supertree construction. On the wider issue of the large-scale distributed computing paradigm, we have highlighted the principal advantages of the paradigm, which are ease-of-use, flexibility, affordability and efficiency.

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