Development and Pilot Evaluation of a High-Performance Computing System for Web-Based Deployment of Pharmacometrics Applications in a Multi-User Training Environment.

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Background

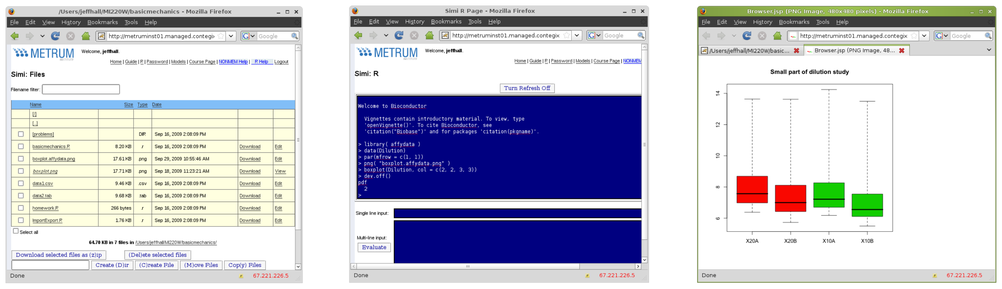
Innovative and adaptable training programs and resources are essential in the effort to train the pharmacometric work force of the future. Given the paucity of existing training programs, available training materials, and academic champions, a virtual faculty and online curriculum coupled with shared high performance computing resources have been proposed as part of the solution to this training problem [1]. In the work described here, a prototype shared high performance computing system is developed, implemented and evaluated in a real-world pharmacometric training environment.

Objectives

1. To design and implement a multi-user, high performance computing (HPC) system for deploying typical pharmacometrics applications over the web, and
2. To evaluate the performance of the HPC system in a real-world pharmacometrics training environment.

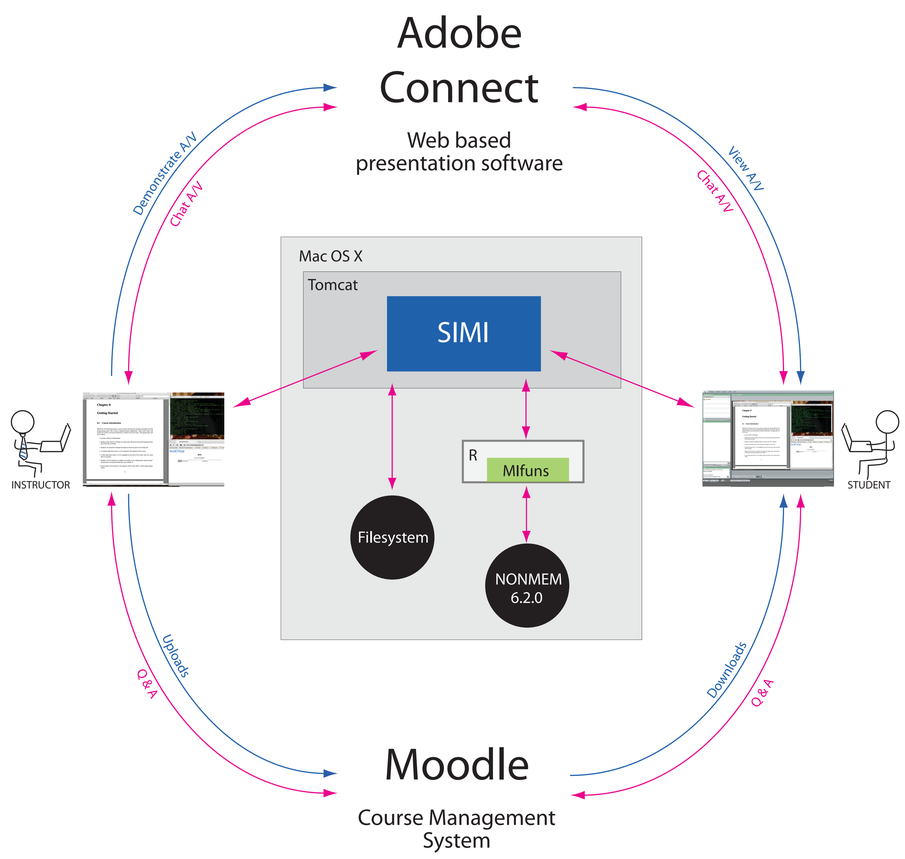
Methods

Requirements for the HPC system and user-interface were defined, including specifications for hardware, operating system, user interface, and pharmacometrics software applications; and a careful object-oriented analysis [2] of requirements was performed. Standard software design and requirements analysis techniques [2, 3] were used to design SIMI (Server Interface from Metrum Instutute). SIMI was written in the Java and Javascript [4] languages, and used Java Server Pages [5]. It employed the OpenSymphony Sitemesh [6] package for site configuration. The system was deployed using the Apache Tomcat webapp container [7]. Hardware consisted of a multi-core, Intel-based, Mac Xserve running OS X Server v. 10.5.



SIMI: Typical filesystem, R session, and graphics output views.

Pharmacometric software applications were installed and qualified, including: R 2.7.2 [8], NONMEM VI, level 2.0 [9] installed with NMQual 6 [10], and the MIfuns package [11]. A Moodle-based educational content management system [12] was also deployed to support the virtual classroom environment [13]. Classes were taught remotely in real time using Adobe Connect web-based presentation software [14]. Pilot evaluation of the HPC system consisted of three test cases: 1) LIU PHS 887: a semester-long introductory pharmacometrics course at Long Island University, Fall 2008, 2) MI210, Essentials of Population PKPD Modeling and Simulation, a semester-long web-based training course at Metrum Institute, Fall 2008 and, 3) MI220, R Programming for Pharmacometrics, a semester long web-based training course at Metrum Institute, Spring 2009. Hands-on HPC applications across all courses included, live demonstrations and simultaneous practice problem execution during class time, weekly homework assignments focused on population pharmacokinetic model development, evaluation and simulation, and a more extensive pharmacometrics project for each student in each semester.



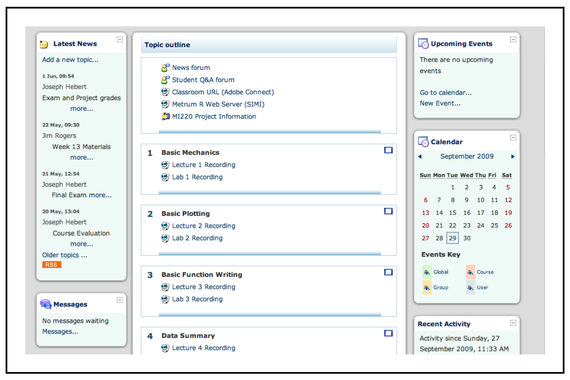
Schematic diagram of tool integration and information flow.

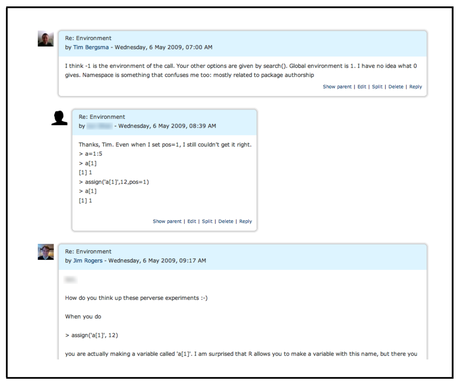
Design goals

- Browser access to file system
- File persistence
- Browser access to pharmacometrics applications via R
- R session persistence
- Transparent authentication
- Consistent and attractive interface
- Minimal software configuration for student
- No technical support required at student's institution
- Minimal interface training for student

Tools used

- MIFuns: an R interface for NONMEM [11]
- NMQual: a package to manage NONMEM installations in a traceable and self-documenting way [10]
- Apache Tomcat: the Apache reference servlet and JSP container [7]
- Moodle: an open source course management system (CMS) [12]
- Adobe Connect: commercial web-based presentation software (web conferencing tool) [14]





Left: *Moodle course page, with links to forums, course materials, presentation software site (Adobe Connect), and computational software site (SIMI).* ***Right:*** *Moodle forum discussion between instructor and students.*

Results

Using the SIMI web interface, a single system administrator was able to expose a consistent pharmacometrics software experience to a diverse group of students, simultaneously at multiple locations. With minimal configuration, this Tomcat-based webapp gave multiple users access to private, persistent R sessions and file space. Training experiences were characterized by consistent use of tools and scripts across all students, and interaction between students, instructors and the HPC system at virtually any time and location. Errors and problems in students exercises were easily viewed and corrected on the same HPC system. The entire class was conducted without the need for IT support at the university. Instructors and students noted a limitation in the current implementaion, which required system administrator intervention to terminate unwanted model runs.

Pilot evaluation of the HPC system verified functionality for three web-cast courses: LIU PHS 887 (Fall 2008); MI210 (Fall 2008); and MI220 (Spring 2009). The system met expectations during live demonstrations and on-line student practice. Class size and consequent server load did not noticeably impact performance, suggesting excess capacity. Further characterization of the pilot evaluation is provided below.

Case	Students	Pharmacometrics Software	Compute Nodes	Jobs Submitted	Run Times	Training Period	Percent Up-time
1. LIU PHS 887	14	R 2.7.2, NONMEM VI, 2.0	8	>500	0.5 to >600 min	3.5 months	100%
2. MI210	32	R 2.7.2, NONMEM VI, 2.0	8	448	0.5 to 120 min	4 months	100%
3. MI220	14	R 2.7.2,	8	1176	0.5 to 5 min	4 months	95%

Performance statistics for test cases.

Conclusion

The HPC system implementation met the design goals. It demonstrated the feasibility of web-based deployment of typical pharmacometrics software, and illustrated the practical application of this system for hands-on pharmacometrics training.

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