POPULATION PHARMACOKINETIC / DYNAMIC MODELING VIA THE WORLD WIDE WEB

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ABSTRACT

A new research resource has been developed, allowing organizations with limited resources for program development to develop large and nonlinear non-parametric population models. The infrastructure described below is flexible, reliable, and secure.

In the first section we give a formulation of the problem, then we give a description of the infrastructure eliminating the problem. The last section contains an example of how this system is being used today.

FORMULATION OF THE PROBLEM

Until now the two main factors limiting the number of non-parametric population models have been the need for extensive computing resources, and the difficult user threshold for accessing such systems The current *de facto* standard for information exchange is the World Wide Web. The interface to the WEB in the form of a browser is almost universally known and used by most researchers on a daily basis. Designing a WEB interface and a corresponding infrastructure to the computing resources effectively eliminates both the need for setting up an individual computing resource and at the same time substantially reduces the high user threshold.

BASIC INFRASTRUCTURE

The implemented architecture is identical to the three-tier architecture found in database systems. However, in this case the database is replaced with a computational machine. The three-tired infrastructure is shown in the figure below:
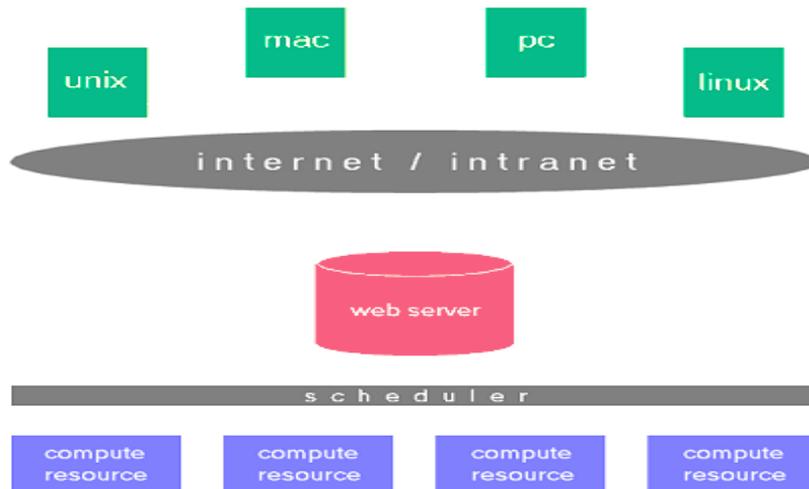
The resources are "glued" together with the "Scheduler", the manager of this system. It is responsible for allocating job resources, starting jobs, keeping track of the job status as the jobs run, and for cleaning up when jobs finish. The Scheduler also provides options for access control, accounting, and more detailed job management. The WEB server is the interface between the end user and the computing infrastructure. Its prime task is to transmit data between the user and the Scheduler, and it also has some logic built in. The logic part is the only place where programming is required.

SELECTED COMPONENTS

The system can be assembled using a broad selection of components, especially the number of WEB servers and Schedulers. In this section we describe the software used in two fully functional systems already operated on a daily basis; one operated by the NPACI, the other by our LAPK group. At present, research organizations in 6 countries use the WEB computing resources.

THE NPACI IMPLEMENTATION

The NPACI consortium has been operating a WEB interface for access to resources such as that developed by the LAPK group over the past several years. That "Gridport" WEB interface gives the user access to a Cray T3E, to the IBM "Blue Horizon" (the world largest academic supercomputer) and to other NPACI resources.

THE LAPK IMPLEMENTATION

The implementation made by our LAPK group is based on freeware products. The only expense is the compilers and the hardware. The system uses the Apache WEB server and servlets for the server logic. The scheduling system is OpenPBS. Currently this system gives users access to an HP Superdome at the University of Oslo, Norway, and to our LAPK Linux Cluster.

The LAPK solution can be considered a down sized version of the NPACI system. It exists as a "boxed" solution and it is offered to organizations who would like to perform in house population modeling.

ACTUAL USE OF THE SYSTEM ILLUSTRATED BY A NOVEL NON-LINEAR CICLOSPORINE PK-MODEL.

Ciclosporine (CYA), a drug who's main use is as an immuno-suppressant after organ transplantation, has a relatively narrow margin of safety, and its use commonly involves therapeutic drug monitoring (TDM). Despite such efforts, the drug has nevertheless proved difficult to control. The drugs plasma concentration time profile typically display a very marked and sharp peak with levels decreasing very rapidly thereafter.

Such rapid and vigorous variability will in general add complexity to the minimum pharmacokinetic model set up to describe the drug's mass transport within the body. In the case of ciclosporin, this situation is further aggravated by a complex non-linear absorption from the gut.

FORMULATION OF THEORAL.– CYA MODEL

CYA pharmacokinetics after p.o administration was formulated as a three (gut, central and peripheral) compartment model with linear elimination from the central compartment, linear exchange between the central and peripheral compartment, and a non linear time dependent absorption from the gut to the central compartment.

The absorption was expressed as a function involving a time dependent fraction described by the cumulative Weibull function as follows:

$$WB = ka(1 - e^{-[(\frac{T}{A})^B]})$$

RUNNING THE MODEL WITH THE LAPK WEB COMPUTING RESOURCE

After this non-linear model was formulated and transformed to Fortran code on a PC, using the USC*PACK Boxes program, the model file and the instruction file containing patient data (dose, covariates, blood concentrations of CYA and times) were sent to the central computer via the LAPK web-computing homepage. This 2-step operation, including providing information about where to send the resulting output, is performed as a simple and very familiar browse and click procedure. The initial response is to show the user if the model is being computed or alternatively if it is queued, waiting for resources to become available. The user can, if he or she wishes, keep track of the progress of the computing by directly viewing the output files online. Eventually, when the job is finished, the user will be notified by e-mail, with the results attached as a single self-extracting archive.

CONCLUSION

The introduction of a WEB interface for the LAPK non-linear population model programs allows more people to generate such models. Accessing the programs is now much simpler, and the programs are available to every researcher that has a connection to the Internet.