

Dear Colleague:

Thank you for your inquiry concerning our work. I am enclosing some material describing our laboratory and its software, the USC*PACK PC clinical programs, the IT2B and NPDM population modeling programs, and the BOXES program for making large nonlinear and effect pharmacokinetic/dynamic models. I am also enclosing a description of our approach to the development of optimal, target-oriented, model-based, individualized drug dosage regimens, and an academic licensing agreement to use the programs.

The USC Laboratory of Applied Pharmacokinetics is also pleased to announce five new PK/PD workshops for the first half of 2002. They are:

1. January 24-26, in Pamplona, Spain (a hands-on workshop)
2. February 21-23, here at USC (also a hands-on workshop)
3. March 19-22, in Turin, Italy (also a hands-on workshop)
4. April 8-12, in Moscow, Russia [registration]
5. May 15-17, in St. Petersburg, Russia [registration]

More information about these workshops can be found on our web site, www.lapk.org

Back to the software. The USC*PACK clinical programs employ a linear 3 compartment pharmacokinetic model having an absorptive, a central (serum) compartment, and a peripheral (nonserum) one. One can also enter and store parameter values for any drug having this basic structural model. There are population models available for clinical use to guide and adjust therapy with gentamicin (general medical patients, ICU patients, others, and several for newborns and premies). Similar models are available for Tobramycin, Netilmicin, and Amikacin. There are also models for digoxin, digoxin with quinidine, quinidine, and digitoxin. The software also permits development of dosage regimens to achieve target goals in the peripheral nonserum compartment as well as to achieve target serum concentration goals. This is especially useful for digoxin and digitoxin, where the main clinical and toxic effects are correlated much better with those peripheral (tissue) concentrations than with serum concentrations.

Models are also available for lidocaine, theophylline (several different ones for smokers, etc, and for long - acting preparations), vancomycin, trimethoprim, and others.

In the user manual, also available for inspection and printout on line at our web site, http://usc.edu/hsc/lab_apk/ are a number of clinical case presentations (pages 40-50) which illustrate the use of the programs in a variety of clinical situations.

In addition, there are about a dozen Technical Reports available on our web site, on various PK/PD, clinical, and mathematical aspects of pharmacokinetics, population PK/PD modeling, and

clinical applications. You can download them directly, read them, and print them. For some files you will need the Adobe Acrobat reader, which you can also get free from the web links to it.

The USC*PACK clinical programs also let you enter and store population parameter values for any drug having the basic structural model described above. They also employ MAP Bayesian fitting to make individualized pharmacokinetic models, and they also compute AUC, AUIC, AUC/MIC, % of dose interval above the MIC, peak/MIC ratios, etc.

The programs also compute diffusion into porous spherical objects such as endocardial vegetations. These models can also be used to simulate a post-antibiotic effect.

This input, as well as the serum concentration profile, can then be used as input to effect models, of the growth and kill of organisms, for example. In this way one can now evaluate the ability of a certain dosage regimen to generate a serum level profile, and to kill under defined circumstances, in addition to relating growth and kill to the more common indices such as AUC, time above MIC, AUC/MIC, etc.

The software for population pharmacokinetic modeling employs both parametric (iterative 2-stage Bayesian, IT2B) and nonparametric EM (NPEM) methods. Again, the basic structural model is the same. Many menus are available for parameterizing this 3 compartment linear model in many ways (rate constants, clearances, etc.).

Other much larger and quite nonlinear PK/PD population models (any system which can be described by ordinary differential equations) can now be made using the IT2B and NPEM approaches on the Cray T3E and the new IBM Blue Horizon large parallel machines at the San Diego Supercomputer Center. The Blue Horizon has 1152 processors, and is the fastest academic machine available for nonclassified work. Research accounts on the Blue Horizon can be obtained upon request and approval. The BOXES program can be used to aid in preparing the differential equations for these large and nonlinear models.

The software is made available by license from the University. The requested donations for this version, whether or not you are already a USC*PACK user, are:

	Hospital or Academic Institution	Commercial or Industry
First donation:	\$395.00	\$695.00
Upgrades thereafter:	\$295.00	\$495.00

However, upgrading to the present version from version 10.6 or 10.7 is free.

We can handle checks or electronic bank transfers (ask us for info), but not credit cards or purchase orders. Please sign and mail the enclosed license agreement to use the programs back to us, along with a check for the appropriate amount, made out to the University of Southern California. We will send the programs back to you with the user manual and other material as soon as possible. We supply the programs on HD 3.5 inch floppy disks, and also on CD's.

The programs run in Windows 95, 98, NT, or 2000 in the DOS mode. They need about 610K free memory (the less memory-resident software you have, the better), and need about 20 Mb free disk space to install.

If you have any problems or questions at any time, please write to the return address, call us at 323/442-1300, fax us at 323/442-1302, or email us at jelliffe@hsc.usc.edu. We are also on the World Wide Web at http://www.usc.edu/hsc/lab_apk/. This site has announcements of new events, new upgrades for some of the software which you can download, and a number of publications and technical reports.

Sincerely,

Roger Jelliffe, M.D.
Professor of Medicine

THE USC*PACK PHARMACOKINETIC PROGRAMS

WHAT'S NEW IN THE SETUP! CLIENT - SERVER MODES

The programs now run in 3 modes. The first is the usual mode on a single machine. The second is on a network, in a classroom mode. Each classroom machine accesses the programs from the network, but keeps its patient data files in its own disk or directory. The third is a true client-server mode. Here, all programs and patient data files are kept on the central hospital server, for example, but are accessed and run from the satellite (client) machines.

WHAT'S NEW WITH AMINOGLYCOSIDES

These programs have several new population PK models, for general medical patients, ICU patients, young previously healthy patients, for gentamicin in patients with spinal cord injuries, and for newborn infants. As before, the GENTamicin, TOBramycin, NETilmicin, and AMIKacin programs compute D-optimal times for monitoring serum levels. Diffusion into vegetations and models of bacterial growth vs killing at a stated MIC can also be evaluated as described just below.

WHAT'S NEW WITH GENERAL MODELING, BAYESIAN FITTING

The General Modeling, Bayesian fitting program has an option for entry of a chronic steady-state dosage regimen, followed by subsequent changes in dosage or renal function. Other related programs compute the dynamics of diffusion into a spherical simulated endocardial vegetation, abscess, or a bacterium, nonlinear saturable pharmacological effects, and the dynamics of bacterial growth and kill, and the post-antibiotic effect (PAE). These help to evaluate the efficacy of antibiotic regimens with respect to their ability to kill adequately under various circumstances, for various values of an organism's MIC. Models for simulating a PAE of 6 hours,

and for growth and kill of *Pseudomonas* by gentamicin, tobramycin, and ticarcillin are now provided. You can also make and store your own models.

WHAT'S NEW WITH THE IT2B AND NPEM POPULATION MODELING PROGRAMS

The IT2B and the NPEM programs have been very much overhauled and upgraded. The NPEM program now automatically helps you select an appropriate number of grid points to support your population joint density. It has algorithms to make each computational cycle go progressively faster. The 2D plots of the marginal and the 3D plots of the joint marginal densities are enhanced. Scatterplots and regression relationships are now available for predicted versus measured serum levels in both the Iterative 2 Stage Bayesian (IT2B) population modeler, from mean or median population parameter values. Each patient's own Bayesian posterior parameter values can also be used to predict the measured levels.

For the NPEM part, one similarly can predict measured serum levels from population mean, median, or mode values, and can also further compute each patient's individual Bayesian posterior parameter joint density, and can see the predicted versus measured serum levels based now on each patient's own mean, median, or mode parameter values.

There are now also new versions of the IT2B and NPEM programs that permit making large and nonlinear PK/PD models. These use a new version of the BOXES program which greatly enhances the development of the differential equations describing the behavior of the model, the multiple output equations for the model, and the parameter names. The user then accesses the Cray T3E or the new IBM parallel computer at the San Diego Supercomputer Center, gets the relevant files from his PC, does the analysis, and sends the result files back to his PC to examine them.

THE OVERALL USC*PACK COLLECTION NOW INCLUDES:

1. The USC*PACK CLINICAL programs. These enhance precise goal-oriented dosage design and therapeutic drug monitoring by Bayesian individualization of drug dosage regimens. Drugs include aminoglycosides, vancomycin, digoxin, digoxin with quinidine, digitoxin, lidocaine, procainamide, theophylline, quinidine, gentamicin in newborns, and TMP-SMX for PCP pneumonia. CCr is computed between a single stable or pairs of unstable serum creatinine levels. It can change from dose to dose, as can body weight. Models of diffusion and bacterial growth and killing are especially useful to evaluate adequacy of a regimen to kill under stated conditions of growth rate, max kill rate, and MIC.
2. The USC*PACK IT2B and NPEM POPULATION pharmacokinetic modeling programs employ an iterative Bayesian and a nonparametric expectation maximization (NPEM) algorithm respectively. The strength of the NPEM program is that it computes the entire joint probability density for a 2 compartment absorptive model, or larger on the SDSC Cray T3E, even with mixed oral and intravenous input, and thus can obtain both Vd and bioavailability together. It makes no parametric assumptions such as mean, standard deviation, etc., but also gets them. It can thus discover unrecognized subpopulations. It reads routine patient data files from the clinical programs. Parameter values found can be entered and stored for use with the clinical programs.

3. The USC*PACK BOXES program makes customized PK/PD models by placing boxes on the screen and connecting them with arrows. Equations are automatically written for the Model part of the ADAPT I PC programs. Effect models (Hill or Keo) are easily made.

The programs run on the IBM PC and compatible machines. They need at least DOS 5.0, and 16 MB of memory. The programs come on 3.5 inch disks. Please sign and mail the enclosed license agreement back to us, with a check, made out to the University of Southern California. We will send the programs as soon as possible. If you have questions, write to us at 2250 Alcazar St., Los Angeles CA 90033, call us at 323/442-1300, fax us at 323/442-1302, or email us at jelliffe@hsc.usc.edu. We are also on the World Wide Web at http://www.usc.edu/hsc/lab_apk/ It has announcements of new events and developments, and publications.

Sincerely,

Roger Jelliffe, M.D.
Professor of Medicine

The licensing agreement from USC to use the software is shown below.

**LABORATORY OF APPLIED PHARMACOKINETICS
USC School of Medicine (CSC 134B), 2250 Alcazar St., LA, CA 90033 Phone (323) 442-1300, Fax (323) 442-1302
ACADEMIC LICENSE AGREEMENT (Version 9/12/98)**

This Agreement is made between ("Researcher") and the University of Southern California ("University"), University Park, Los Angeles, California 90089, with respect to computer software developed under the direction of Roger W. Jelliffe, M.D., a U.S.C. faculty member, for use in studying drug behavior and calculating probable drug dosage and infusion requirements for patients and supporting documentation (both of which are herein referred to as "Software"). The University has the sole right to license use of the Software, and is willing to grant a royalty-free license to the Researcher to use the Software for research purposes under the following terms. The Researcher realizes that the Software may be of significant commercial value to the University, and Researcher desires to evaluate, test and use the Software listed at the bottom of this document for research purposes only.

1. This License is limited to use of the Software for academic and research purposes by the researcher within the institution designated below, and will not be disclosed, given or sold to anyone outside of the institution. Duplication of the Software for any purposes other than the above use, and for back-up protection, is prohibited. The Software may not be used for any commercial purpose without the express written agreement of the University. Researcher will return Software and destroy all other copies immediately upon request.

2. Researcher further acknowledges that this agreement will also apply to all subsequent Software s/he may receive from Dr. Jelliffe unless another written agreement is concluded. All Software is and will remain the property of the University.

3. Researcher acknowledges that the Software is directed to pharmacokinetic analysis and the control of drug dosage regimens. Researcher understands that the University makes no warranties, either express or implied, as to any matter concerning this Software, including the condition of the Software, its usability, or fitness for any particular purpose. Researcher agrees to hold the University, its officers, employees and agents, including but not limited to all individual developers of the Software, harmless for any and all damages, expenses, claims or other liability suffered as a result of Researcher's use of the Software. Researcher agrees that s/he alone is responsible for whatever dosage regimen s/he or his/her groups order for or administer to a patient.

4. This Agreement constitutes the entire Agreement between the parties concerning the Software. No amendment or assignment shall be binding on the parties unless mutually agreed to and executed in writing by each of the parties. This Agreement shall be interpreted in accordance with the laws of the United States and of the State of California. Jurisdiction and venue shall lie with any competent court within the County of Los Angeles, California. In the event litigation or arbitration is commenced to enforce any of the terms of this Agreement, the prevailing party shall have the right to recover its reasonable attorneys' fees and costs of such litigation or arbitration from the other party.

SOFTWARE LIST:

(The USC*PACK PC Clinical Collection)

1. GENT
2. TOB
3. NET
4. AMIK
5. MB
6. MLS

(The USC*PACK Modeling Collection)

1. MODEL, ID, ODE, SIM
2. MMID8, MMSIM8
3. ID3, SIM3, ID3CCR
4. ID3P, SIM3P,
5. BOXES
6. IT2B and NPEM Population Programs

Date: _____ Researcher (Please print or type): _____

Institution: _____

Address: _____

City, State Zip Code: _____

Country: _____

Phone: _____

Fax: _____

Email: _____

Please check Type of User: Hospital or Academic _____ Commercial or Industrial _____

Signature _____ Date _____