AAPS MODELING AND SIMULATION FOCUS GROUP NEWSLETTER

http://www.aapspharmaceutica.com/resources/focus/computer.html

Issue 1 – NOVEMBER 2001

WELCOME!

We have decided to try a newsletter format to keep you all up to date as to what's happening in M&S within AAPS and other societies and disciplines.

FOCUS GROUP SCOPE AND LEADERSHIP STRUCTURE

This Focus Group is dedicated to the promotion and increased utilization of modeling and simulation in pharmaceutics and clinical pharmacology. The goals of the group are to promote modeling and simulation-related topics at the Annual Meeting, create workshops related to M&S in drug development, and provide a forum within AAPS for M&S-related discussions, exchange of ideas and experiences and promotion of M&S good practices. The Focus Group Chair is Peter Bonate, with Ilex Oncology Inc., San Antonio, TX; the Focus Group Co-Chair is Paolo Vicini, from the University of Washington, Seattle, WA.

UPCOMING MEETINGS AND DEADLINES

We will post here relevant meeting notices a few months in advance, together with the abstract deadline.

- **January 28-29, 2002** — Rescheduled Date: *AAPS Short Course on Computer Simulation and Its Role in Drug Development Research*, Crystal Gateway Marriott, Arlington, VA, register at http://www.aapspharmaceutica.com/
- **November 10-14, 2002** – *AAPS Annual Meeting and Exposition*, Metro Toronto Convention Centre, Toronto, Ontario (Canada)

WHAT'S COOKING FOR THE 2002 AND 2003 AAPS ANNUAL MEETINGS?

Nothing has been set in stone yet – contact Pete or Paolo if you have any ideas for 2003!

RECENT PUBLICATIONS IN M&S

- Baker D, and Sali A. Protein structure prediction and structural genomics. *Science*. 2001 Oct 5;294(5540):93-6.
- Higgins G et al. Final report of the meeting "modeling & simulation in medicine: towards an integrated framework". July 20-21, 2000, National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA. *Comput Aided Surg*. 2001;6(1):32-9.
- Lesko LJ, and Atkinson AJ Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. *Annu Rev Pharmacol Toxicol*. 2001;41:347-66. Review.
- Nagao M et al. Fractal analysis of cerebral blood flow distribution in Alzheimer's disease. *J Nucl Med*. 2001 Oct;42(10):1446-50.
- Nestorov I et al. Modeling and stimulation for clinical trial design involving a categorical response: a phase II case study with naratriptan. *Pharm Res*. 2001 Aug;18(8):1210-9.

M&S ON THE WEB: NEW & INTERESTING SITES

- *Air Force Agency for Modeling and Simulation*, a field operating agency created in June 1996 to coordinate the Air Force's growing requirements for M&S, http://www.afams.af.mil/
- *Modeling and Simulation*, the publication of The Society for Modeling and Simulation International (formerly The Society for Computer Simulation), http://www.modelingandsimulation.org
- *The National Center for Simulation*, a nonprofit corporation focused on M&S, http://www.simulationinformation.com
- *The Society for Computer Simulation International*, a society devoted to the advancement of simulation and allied computer arts in all fields and to facilitating communication among professionals in the field of simulation, http://www.scs.org/.

APPLICATION NOTE: SIMULATING MULTIVARIATE DISTRIBUTIONS

Sometimes it is of interest to simulate data from a multivariate normal density. While many software programs have functions that allow to generate Gaussian random scalars, such as randn in MATLAB, one

would often like to generate random entries that are correlated. To do that, one can perform the Cholesky factorization of the covariance matrix. This is done in MATLAB by the command chol. R = CHOL(X) produces an upper triangular matrix R so that R'*R = X. The Cholesky factor is a matrix analog of the square root: thus, if a vector of independent random numbers is multiplied by the Cholesky factor of a certain covariance matrix, the result will be a random sample from a distribution with that same covariance matrix.

For example, if we want to generate 1,000 samples from a bivariate normal distribution with means 1 and 2 and covariance matrix with unitary variances and –0.5 covariance, we can write the following MATLAB script:

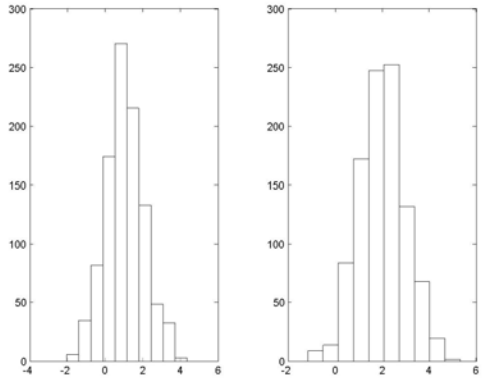
```
Average = [1 2];
Covariance = ...
   [1 -0.5
   -0.5 1];

N = rank(Covariance)
Nsimulation = 1000;

CholFactor = chol(Covariance);
Realization = zeros(N, Nsimulation);

i=1;
while i<Nsimulation+1
  RandomVector = randn(1,N);
  StanDeviation=CholFactor'*RandomVector';
  Realization(:,i) = Average'+StanDeviation;
  i=i+1;
end

mean(Realization')
cov(Realization')
```

The output generated by MATLAB is:

```
>> simulation
N =
     2
ans =
    1.0261    2.0242
ans =
    1.1077   -0.5708
   -0.5708    1.0365
```

As you can see, the arithmetic average and the sample covariance from the 1,000 samples are remarkably close to the ones used to simulate the data. This is a sanity check on our simulation. The distributions of the two variables can also be plotted as histograms using the MATLAB commands:

```
figure(1)
subplot(1,2,1), hist(Realization(1,:))
subplot(1,2,2), hist(Realization(2,:))
```



One last note: while randn generates Gaussian random numbers, rand generates uniformly distributed random numbers! Be careful about using the one you want for your simulations!

Interested in helping out?

You could write an application note, or send ideas for planning the next Annual Meeting, or recently published articles of interest. Just send article citations, world wide web links and whatever you think could be of relevance to the focus group members to vicini@u.washington.edu for inclusion in future issues of this newsletter.

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