

Implementación de un sistema de análisis PK/PD en un departamento de Farmacología Clínica

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Antecedentes



Análisis datos farmacocinéticos/farmacodinámicos

- No compartimental
- **Compartimental**

- Análisis individual: Winnonlin (Phoenix), Adapt
 - Variabilidad residual

- Análisis poblacional: Adapt, Winbugs, Phoenix+NLME, Monolix, NPEM, NONMEM
 - Variabilidad interindividual + Variabilidad residual

Análisis poblacional



FDA

- Guidance for industry. Population Pharmacokinetics. Febrero 1999.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf>

EMA

- Guideline on reporting the results of Population Pharmacokinetic Analyses.
Enero 2008.
<http://www.emea.europa.eu/pdfs/human/ewp/18599006enfin.pdf>

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Descripción NONMEM



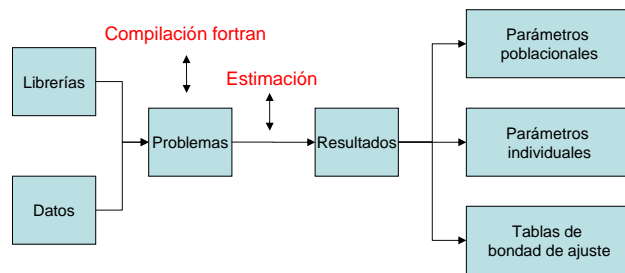
- NONMEM: **NON**-linear **Mixed Effects Modeling**
- Es el software estándar de la industria farmacéutica para el análisis poblacional farmacocinético (PK) / farmacodinámico (PD).
- Desarrollado por la UCSF desde 1979 y actualmente comercializado por ICON, proveedor mundial de servicios en el desarrollo de fármacos.
- Consta de varias librerías de modelos PK y PD compiladas en FORTRAN.

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Descripción NONMEM (cont)



NONMEM **“traduce”** las características del modelo PK/PD definidas por el usuario y calcula parámetros poblacionales e individuales mediante los módulos de optimización de ecuaciones diferenciales de FORTRAN (LSODA) .



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Ejemplo de Librería Control, Datos y Proceso de Estimación



```

run57.mod - Bloc de notas
Archivo Edición Formato Vistas Ayuda
SERIE PKPD MODELING OF ANC AFTER ZALIPHSIS (PNLGA) ADMINISTRATION
$INPUT
STUD ID, HED, AMT, RATE, CRT, TIME, ANC, DV, EVSD, MDV, CYCL, SMF
@COC V1, K10, K12, K21, K13, K31
$DATA ..\MBOC_ANC_PV_TULOR.CSV IGNORE=...
$SUBROUTINE ADVAN6, TOL=4
$MODEL
COMP = (CENTRAL,) 11
COMP = (PERIP1,) 12
COMP = (PERIP2,) 13
COMP = (CIRC,DEPORES) 14
COMP = (SENS,) 15
COMP = (DELAY1,) 16
COMP = (DELAY2,) 17
COMP = (DELAY3,) 18
COMP =
$PK
FIRST
COMMON
INTEGER
IMAX=150000000
IF (MGT.EQ.0) MTC=70
IF (MGT.GT.0) MTC=MGT
DINRY=(THETA(1)**MTC)
  
```

Librería control

Datos



```

run57.MBOC - MBO3
PARAMETERS = 0.1918E+01 0.1102E+01 0.1048E+01 0.2215E+00 0.1373E+02 0.7791E+01
COC V1 = 0.1487E+00 0.1547E+00 0.6817E+01 0.7502E+00
K10 = 0.2512E+00 0.3417E+01
K12 = 0.1972E+00 0.1972E+00 0.1939E+02 0.8471E+01 -0.3491E+01
K21 = 0.1972E+00 0.1972E+00 0.1939E+02 0.8471E+01 -0.3491E+01
K31 = 0.1972E+00 0.1972E+00 0.1939E+02 0.8471E+01 -0.3491E+01
CIRC,DEPORES = 0.4004E+00 0.1407E+00 0.13790E+00
SENS = 0.4182E+01 0.9017E+01 0.1442E+01 0.7907E+01
DELAY1 = 0.2512E+00 0.3417E+01
DELAY2 = 0.1972E+00 0.1972E+00 0.1939E+02 0.8471E+01 -0.3491E+01
DELAY3 = 0.1972E+00 0.1972E+00 0.1939E+02 0.8471E+01 -0.3491E+01
MTC = 70
MGT = 0
  
```

Estimación

- Especificaciones:
- Sistema de código configurable
 - Entorno MS-DOS, admite procesos por lotes
 - Estimación: compilador y arquitectura procesador dependiente

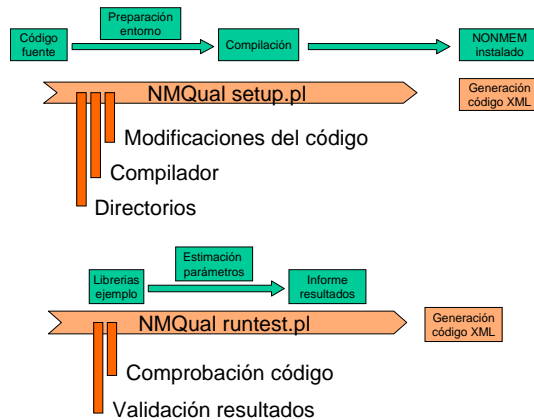
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Validación de NONMEM



NMQual

<http://www.metruminstitute.org/index.php>



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Ejemplos de uso de NONMEM en otras compañías



Mechanism-based Pharmacokinetic/ Pharmacodynamic Meta-analysis of Trabectedin (ET-743, Yondelis) Induced Neutropenia

J Hing¹, JJ Perez-Ruizo^{2,3}, K Stuyckens², A Soto-Matos⁴, L Lopez-Lazaro⁴, P Zannikos⁴

PK/PD model development. *Software:* Population PK/PD modeling of neutropenia after trabectedin administration was performed using NONMEM[®] (University of California, San Francisco, CA) version V, level 1.1, NM-TRAN version III, level 1.0, and PREDPP version IV, level 1.0 (GloboMax, Hanover, MD).³⁵ NONMEM analyses were performed on the Johnson & Johnson Computational Grid, which is based on the United Devices' Metaprocessor product running with an Oracle 9i repository, and a mixture of Intel-based processing nodes running Microsoft Windows and Red hat Linux operating systems. The Johnson & Johnson Computational Grid executes NONMEM models using Intel Fortran 9.0 for Windows as a compiler.

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Ejemplos de uso de NONMEM en otras compañías



GLAXOSMITHKLINE: Implementing Breakthrough Technology for Clinical Development Modeling and Simulation

THOUSANDS MORE MODELS RUN WITH HUNDREDS
OF HOURS SAVED

Within days, the team's PK/PD analysis software (NONMEM from GloboMax) was up and running on the 1500-node Windows grid. An internal GSK team grid-enabled the application themselves using Univa UD's flexible APIs for application enablement. GSK can now run thousands of models concurrently, and the grid manages the scheduling of these runs depending on the resources best suited (and available) for the work.

Execution of jobs on the grid is transparent to the user – he/she only knows that a job run is submitted to NONMEM and results come back a great deal faster than before. The Research, Modeling and Simulation team now assess six to eight thousand models per analysis compared to the one to two hundred that were previously possible when analysts wrote the required code one model at a time. What used to take months can now be done in weeks.

<http://www.univaud.com/about/resources/files/cs-gsk.pdf>

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Plataformas para creación del clusters



Soluciones estudiadas:

- **Piraña** (<http://sourceforge.net/projects/pirana>)
- **Platform LSF** (<http://www.platform.com/Products/platform-lsf>)
- **Univa Uniclust** (<http://www.univaud.com/hpc/products/uniclust/>)
- **Sun Grid** (<http://www.sun.com/software/sge/>)

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Sistemas para ejecución de NONMEM



Compiladores fortran estudiados:

- G77
- Gfortran
- Sun
- Intel

Distribuciones Linux estudiadas:

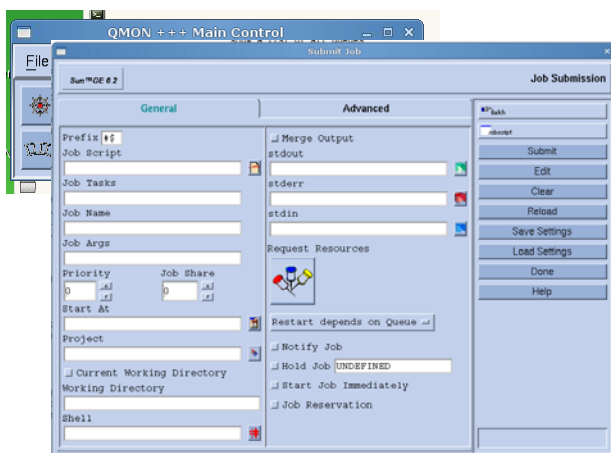
- Ubuntu 8.10 workstation
- Ubuntu 8.10 server
- Debian 4
- OpenSuse x64 11.1

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Monitor de status del Cluster



•Qmon



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Acceso al cluster desde Windows



Acceso a terminal remoto: FreeNX

<http://www.nomachine.com/download-client-windows.php>

Acceso a datos:

Instalación servicio Samba

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Integración del cluster en PsN



Perl speaks NONMEM

<http://psn.sourceforge.net>

Opciones comunes:

-run_on_sge	Default not used. Use Sun Grid Engine queueing system.
-sge_queue='string'	Default empty. Only valid with -run_on_sge. Maps to qsub option -q
-sge_resource='string'	Default empty. Only valid with -run_on_sge. Maps to qsub option -l

Ejecución:

```
execute run1.mod run2.mod run3.mod -run_on_sge
```

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Algunos scripts de PsN



Programs/scripts available in PsN

- psn** List available PsN scripts.
- psn_options** List options common to most PsN scripts.
- execute** NONMEM runs are started using one or multiple model files.
- bootstrap** Non-parametric bootstrap using the percentile or BCa method.
- sse** Stochastic Simulation and Estimation
- npc** Numerical Predictive Check
- vpc** Visual Predictive Check
- cdd** Case Deletion Diagnostics
- llp** Log-Likelihood Profiling around maximum-likelihood parameter estimates.
- scm** Stepwise Covariate Model-building
- sumo** Summary of Output from NONMEM
- update_inits** read final THETA, OMEGA and SIGMA estimates from a NONMEM output file and put into a given model file.

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Resultados y Conclusiones



- NONMEM VI es totalmente funcional bajo la distribución OpenSuse empleando el compilador gfortran
- Creación de un cluster mediante SunGrid
- Acceso al sistema sencillo desde Windows empleando FreeNX para visualizar la pantalla remota, y el servicio Samba para acceder a los datos mediante red
- Integración de PsN con Sungrid, facilitando en gran medida la ejecución y organización de problemas
- Todo el software empleado, a excepción de NONMEM es libre

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