A Comparison of a Genetic Algorithm-Based Automated Search Algorithm to Standard Stepwise Approach for Population Pharmacokinetics using NONMEM

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Objective

To compare, using the AIC, the selection of model structures, covariates, covariate relationships, and error structures in models chosen for five separate drugs using both stepwise or genetic algorithm (GA) approaches.

Introduction

- Model search strategies in pharmacokinetic/pharmacodynamic (PK/PD) modeling involve numerous decisions from the modeler
  - ⋆selection of the appropriate model structure (compartments and parameterizations)
  - ⋆covariates and covariate relationships
  - ⋆error structure selection
- Discrete search space which can not be fully evaluated using conventional approaches
- Initial model structure and order of covariate inclusion can influence downstream results (Wade *et al.* 1994)
  - ⋆error structures (additive, proportional)
  - ⋆covariate relationships (proportional, power-law, Michaelis-Menten, Hill)
  - ⋆addition of covariates and error relationships are not necessarily linear in reducing error
- Exploration of entire search space is impractical due to time constraints
- GA approach may help address these issues (Bies *et al.* 2006)
  - ⋆capable of running without direct supervision
  - ⋆criteria for assessing model accuracy essential

Methods

- The following drugs were evaluated: citalopram, perphenazine, olanzapine, quetiapine, and risperidone

Table 1: Data and stepwise model summary for the five compounds

Compound	# patients	# data points	Model structure	Covariates
citalopram	331	1324	2-comp., intravenous combined error	10
perphenazine	156	421	1-comp., oral proportional error	8
olanzapine	523	1527	1-comp., oral additive error	7
quetiapine	405	945	1-comp., oral additive error	7
risperidone	490	1236	1- or 2-comp. mixture model, intravenous combined error	7 3 CL groups

- Search space was restricted to those originally considered during the initial model evaluation
  - ⋆all model structures (compartments and/or mixtures), covariates, covariate relationships, and output error metrics
  - ⋆6 relationships for continuous covariates and 4 for discrete covariates
  - ⋆3 interindividual variability structures (exponentiated, proportional, additive)
  - ⋆3 residual unknown variability structures (additive, proportional, combined)
  - ⋆risperidone analysis included a mixture model option
- Example code with token sets shown below

```
Number of models =
1
########## Begining of model # 1 ############
$PROB GA COVARIATE SEARCH 1CPTMOD OLANZAPINE COMBINED

$INPUT ID DATE=DROP TIME AMT RATE DV MDV CMT SS II SEX SMOK AA AGE WT

$DATA FINALDATASET8.CSV

$SUB ADVAN=ADVAN2 SS=SS2 TRANS2

$PK

    TVCL5 = THETA(1)
    TVCL4 = TVCL5 COVSEXCL(1)
    TVCL3 = TVCL4 COVSMOKCL(1)
    TVCL2 = TVCL3 COVAACL(1)
    TVCL1   = TVCL2 COVAGECL(1)
    TVCL = TVCL1 COWTCL(1)
    CL    = TVCL CLERR(1)
    TVVE = THETA(2)
    TVVD  = TVVE COVSEXV(1)
    TVVC = TVVD COVSMOKV(1)
    TVVB = TVVC  COVAAV(1)
    TVVA = TVVB COVAGEV(1)
    TVV = TVVA COWTV(1)
    V    = TVV VERR(1)
    TVKA = THETA(3)
    KA    = TVKA
    S2    = V

  IF(MDV.EQ.0.AND.TIME.GE.0.AND.TIME.LE.24) THEN
    PPCI = 1
  ELSE
   PPCI = 0
  END IF
  RP = IREP
$ERROR
    Y=F RESERR(1)
    IPRED=F
    OB = DV ; FOR NPDE PROBLEM 1
    Y= F RESERR(1)
    FSIM = Y ; FOR NPDE PROBLEM 2

$THETA
    (1,18,50)   ;CL COEFF
    (100,3000,8000)   ;V COEFF
    (0.05,0.5,5)     ;KA
    COVSEXCL(2)
    COVSMOKCL(2)
    COVAACL(2)
    COVAGECL(2)
    COWTCL(2)
    COVSEXV(2)
    COVSMOKV(2)
    COVAAV(2)
    COVAGEV(2)
    COWTV(2)
```

```
                COVAACL
N token sets =
                4
N tokens =
                2
Check syntax =
                False
IS IOV OMEGA =
                False
N IOV OMEGA =
                0
Token set #
                1
Token set #
                2
+AA*{THETA(C)}
{$THETA(C)=}(-4,0.01,4)
Token set #
                3
*(1+AA*{THETA(C)})
{$THETA(C)=}(-4,0.01,4)
Token set #
                4
*EXP(AA*{THETA(C)})
{$THETA(C)=}(-4,0.01,4)
Group stem =
                COVAGECL
N token sets =
                6
N tokens =
                2
Check syntax =
                False
IS IOV OMEGA =
                False
N IOV OMEGA =
                0
Token set #
                1
Token set #
                2
+AGE*{THETA(D)}
{$THETA(D)=}(-4,0.01,4)
Token set #
                3
*(1+AGE*{THETA(D)})
{$THETA(D)=}(-4,0.01,4)
Token set #
                4
*EXP(AGE*{THETA(D)})
{$THETA(D)=}(-4,0.01,4)
Token set #
                5
*{THETA(D)}*AGE/({THETA(E)}+AGE)
{$THETA(D)=}(-4,0.01,4){crlf}{$THETA(E)=}(-4,0.01,4)
Token set #
                6
*AGE**{THETA(D)}
{$THETA(D)=}(-4,0.01,4)
```

Genetic Algorithm

- GA fitness function penalties are shown in Figures 1 and 2
- Fitness of models was evaluated based on penalty function
  - ⋆objective function plus penalties from the options
  - ⋆combination of posterior predictive check (PPC) and normalized predictive distribution errors (NPDE)
  - ⋆AIC, eigenvalues, objective function value, and other criteria
- Downhill search and niche evaluation every 5 generations
- Selection of the next population generation was based on a random selection from the previous generation, weighted according to fitness function values
- Niche membership selects all model pairs differing by $< N$ bits
  - ⋆all bit combinations between the top models within a niche are then evaluated
- Model with the highest fitness carried to the next generation
- First-order estimation with interaction for all models
- NONMEM VI with Intel Fortran (VERSION 9.1)
- Performed on 10 Dual Core Computers
- GA search summary and search convergence are shown in Figures 4 and 5
- Stepwise versus GA performance was assessed using model predicted AIC

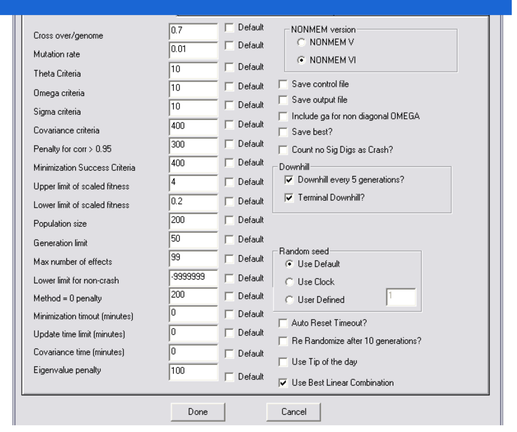

Figure 1: GA fitness function options

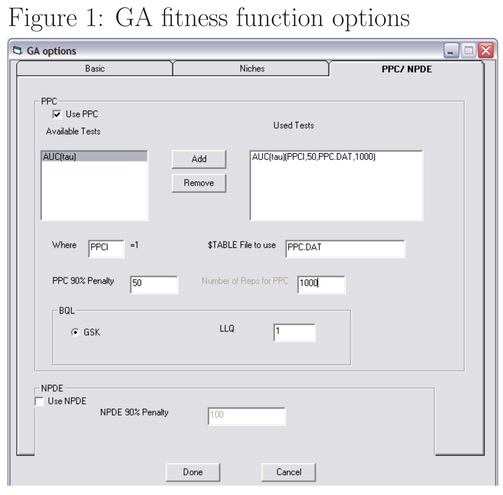

Figure 2: GA PPC and NPDE options

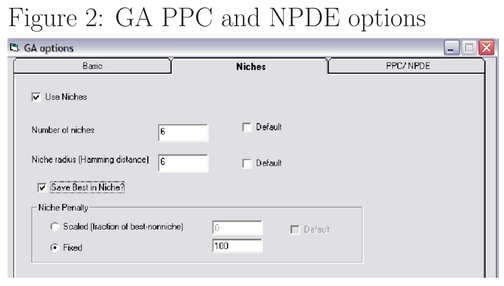

Figure 3: GA niche options

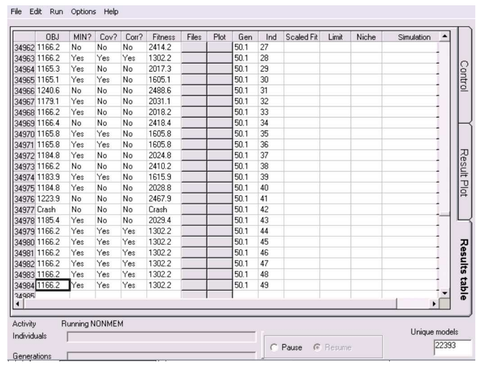

Figure 4: GA search summary

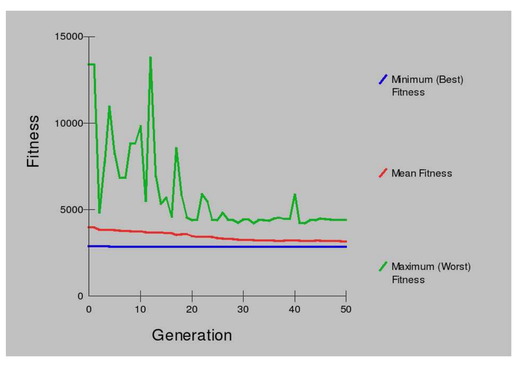

Figure 5: GA search convergence profile

Results

GA versus Standard Approach

Table 2: Summary of model results using both stepwise or GA approaches

Compound	Search	AIC	OBJ	θ	η	ϵ	Covariates	Δ AIC	Comments
citalopram	Step	5713.0	5699.0	8	3	2	CL (weight), Q (fat mass), V_2 (weight, sex)	—	no covariance step
	GA	5345.9	5304.9	17	3	1	CL (sex, weight, body mass index, fat mass) V_1 (sex, body mass index, free fat mass) Q (sex, free fat mass), V_2 (sex, weight, free fat mass)	367.1	covariance step converged
perphenazine	Step	561.9	537.9	12	3	1	CL (race, smoking status, other meds)	—	k_a not estimated
	GA	556.9	531.9	10	1	1	CL (race, # cigarettes, smoking status, other meds) V (age, sex, smoking status)	5.01	covariance step with k_a
olanzapine	Step	10365.8	10347.8	6	2	1	CL (sex, smoking status, race)	—	
	GA	9850.8	9832.8	6	1	2	CL (sex, smoking status, race)	515.0	different error structures
quetiapine	For.	11126	11110.4	4	3	3	V (weight)	—	k_a not well estimated
	GA	10114	10095.7	3	2	2	no significant covariates	1014.7	estimated k_a, no covariates identified
risperidone	Step	5119.1	5103.1	7	5	4	no significant covariates	—	3 CL group mixture model
	GA	4694.9	4662.9	11	3	2	CL (age, sex, race, other meds), V (sex)	424.2	2 CL group mixture model

Risperidone

- GA search included the possibility of one, two, or three groups for parent compound CL
  - ⋆only two CL groups were identified
  - ⋆improvement over the previously developed model
- GA identified significant covariates on CL and V
  - ⋆age, sex, race, and other medications
- Sample code shown below

```
$MIX
P(1)=THETA(3)/(1+THETA(3))
P(2)=1-P(1)
NSPOP=2
$PK
  CALLFL =1
  AAGE = (AGE-46.6)/16.8
  AWT = (WGTB-188)/50
  ASEX = SEX-1
  EST=MIXEST
IF(MIXNUM.EQ.1)THEN
BCL=THETA(4)
ELSE
BCL=THETA(5)
ENDIF
  TVCL1 = BCL *EXP(AAGE*THETA(6))
  TVCL2 = TVCL1 *EXP(ASEX*THETA(7)) *EXP(RACE*THETA(8))
  TVCL3 = TVCL2 *EXP(PARX*THETA(9)) *EXP(FLUX*THETA(10))
  CL = TVCL3 *EXP(ETA(1))
```

```
  TVV1 = THETA(1)
  TVV2 = TVV1 *EXP(ASEX*THETA(11))
  TVV3 = TVV2
  V =  TVV3 *EXP(ETA(2))
  KA=THETA(2)
  ;ADVAN2
  S2=V

  IF(MDV.EQ.0.AND.TIME.GE.0.AND.TIME.LE.24) THEN
    PPCI = 1
  ELSE
   PPCI = 0
  END IF
  RP = IREP
$ERROR
    Y=F *EXP(EPS(1))+EPS(2)
    IPRED=F
    OB = DV ; FOR NPDE PROBLEM 1
    FSIM = Y ; FOR NPDE PROBLEM 2
```

Table 3: Summary of GA population size, generations evaluated, and total number of identified models

Compound	# individuals	# generations	unique models	% total
citalopram	300	49	21431	0.05
perphenazine	300	50	13903	0.35
olanzapine	200	50	8033	0.81
quetiapine	200	50	7231	0.73
risperidone	400	30	7948	0.09

Olanzapine: 3 residual unknown variability, 3 parameters with 3 interindividual variability structures, 5 discrete covariates (4 structures), and 2 continuous covariates (6 structures).
Total # $= 3 * 3 * 3 * 4^5 * 6^2$

Olanzapine

- Same number of parameters and significant covariates
- Differences between the models included
  - ⋆interindividual variability (k_a and CL vs. CL)
  - ⋆output error (additive vs. proportional and additive)
- Estimate of k_a possible with GA

Summary

- GA search resulted in a lower AIC than stepwise for all five drug models
  - ⋆geometric and arithmetic means of 210 and 465
- Different models predicted by the GA for all cases
  - ⋆alternate output error structure (4/5)
  - ⋆different set of parameters with interindividual variability (4/5)
  - ⋆significant covariates/covariate relationships (4/5)
  - ⋆fewer CL categories were necessary in the risperidone mixture model

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