Development and Exploration of Exhaustive, Stepwise and Heuristic Algorithms for Automated Population Pharmacokinetic Modelling

Zhonghui Huang [1] Joseph F Standing [1] Frank Kloprogge [2]

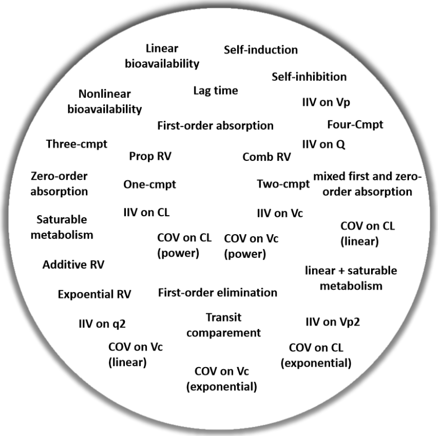
[1]Infection, Immunity and Inflammation Research Teaching Department, UCL Great Ormond Street Institute of Child Health, London

[2]UCL Institute for Global Health, University College London, London, United Kingdom

PAGE 31 2023

Table of Contents

Introduction: Build a Non-Linear Mixed Effect Model



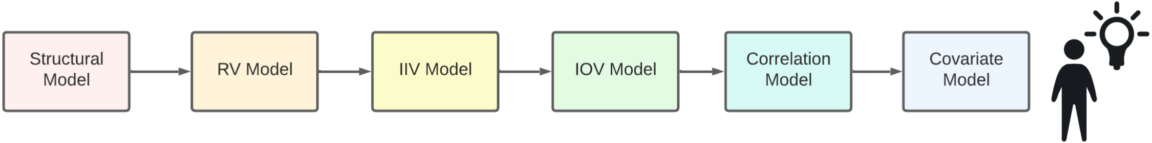
Knowledge base/search space for a PopPK analysis

Questions when build a model:

- First-order absorption?
- Any absorption delay?
- Fixed or linear bioavailablity?
- 1,2,3,4 compartment model?
- Saturable metabolism?
- Random effects on parameters?
- Residual error model?
- Covariate impact? Linear? Power?

Introduction: Human Modelling Strategy

Workflow



Features:

- Decisions made in a sequential manner.
- A locally optimal solution made at each stage.
- Usually no backtracking.

PHARMACOMETRICS

Interaction Between Structural, Statistical, and Covariate Models in Population Pharmacokinetic Analysis

Janet R. Wade,[1,3] Stuart L. Beal,[2] and Nancy C. Sambol[1,4]

Introduction: Inspired from Nature - Genetic Algroithms

A Genetic Algorithm-Based, Hybrid Machine Learning Approach to Model Selection

Robert R. Bies,[1,*] Matthew F. Muldoon,[2] Bruce G. Pollock,[3] Steven Manuck,[4] Gwenn Smith,[5] and Mark E. Sale[6]

Received August 4, 2005—Final January 10, 2006—Published Online March 28, 2006

Application of a single-objective, hybrid genetic algorithm approach to pharmacokinetic model building

Eric A. Sherer · Mark E. Sale · Bruce G. Pollock · Chandra P. Belani · Merrill J. Egorin · Percy S. Ivy · Jeffrey A. Lieberman · Stephen B. Manuck · Stephen R. Marder · Matthew F. Muldoon · Howard I. Scher · David B. Solit · Robert R. Bies

A genetic algorithm based global search strategy for population pharmacokinetic/ pharmacodynamic model selection

Mark Sale[1,2] & Eric A. Sherer[3]

[1]Next Level Solutions, LLC, Raleigh NC, [2]Modeling and Simulation, Kinetigen Inc., Research Triangle Park, NC and [3]Chemical Engineering, Louisiana Tech University, Ruston, LA, USA

Correspondence
Dr Mark Sale MD, Department of Medicine, Indiana University, 1001 West 10th St, W7138, Indianapolis, IN 46202, USA.
Tel.: +1 31 7630 7868
Fax: +1 31 7630 8185
E-mail: mark@nextlevelsolns.com

Keywords
genetic algorithm, NONMEM, pharmacokinetics

Received
28 February 2013
Accepted
4 June 2013
Accepted Article Published Online
17 June 2013

Pharmacometrics

The Journal of Clinical Pharmacology
54(2) 141–149
© 2013, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.176

Genetic Algorithm Guided Population Pharmacokinetic Model Development for Simvastatin, Concurrently or Non-Concurrently Co-Administered With Amlodipine

Ayyappa Chaturvedula, PhD[1a], Mark E. Sale, MD[2], and Howard Lee, MD, PhD[3b]

Population pharmacokinetic model selection assisted by machine learning

Emeric Sibieude[1,2] · Akash Khandelwal[3] · Pascal Girard[2] · Jan S. Hesthaven[4] · Nadia Terranova[2]

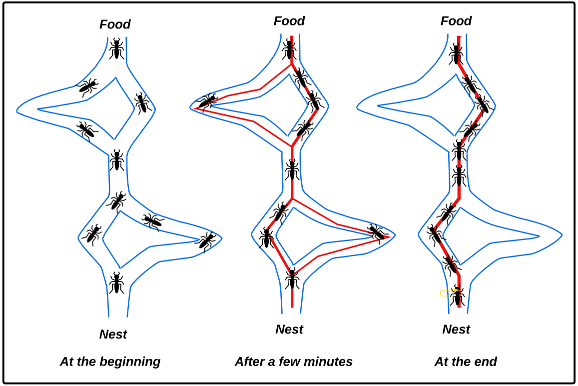
Received: 1 February 2021 / Accepted: 17 October 2021 / Published online: 27 October 2021

Development of a genetic algorithm and NONMEM workbench for automating and improving population pharmacokinetic/ pharmacodynamic model selection

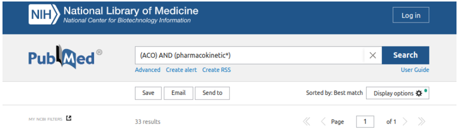
Mohamed Ismail[1] · Mark Sale[2] · Yifan Yu[1] · Nikhil Pillai[1] · Sihang Liu[1] · Beth Pflug[3] · Robert Bies[1,4]

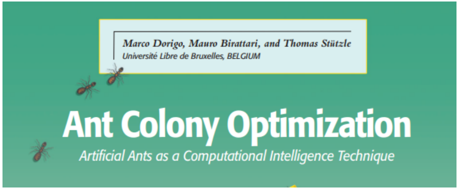
Received: 18 September 2020 / Accepted: 7 September 2021 / Published online: 3 October 2021

Introduction: Inspired from Nature - Ant Colony Optimisation



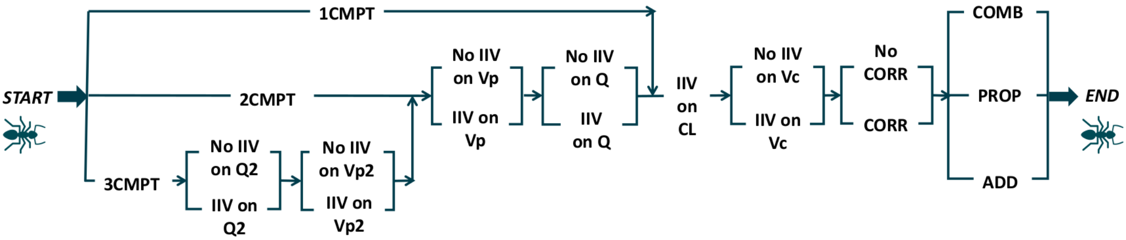
Ant foraging behaviours
Positive Feedback





Introduction: Inspired from Nature - Ant Colony Optimisation

Diagram of ACO path for PopPK analysis



Current evaluation methods for automated modelling

- Limited range of models tested
- Success judged by "better fit" than human model
  - "Better fit" definitions: Lower fitness values
    - Lower AIC, BIC or OFV
    - Lower AIC, BIC or OFV + penalty (convergence, covariance step, shrinkage...)
- Fitting all possible models ("exhaustive approach") allows finding the true best model given the data (not usually done)

Aim and Objectives

How do automated modelling algorithms perform for selecting a “true best model”?

Objectives

- Generate 1,2 3 compartment with different random and residual models (72 cases)
- Fit All possible models (exhaustive algorithm $\Longrightarrow$ ground truth)
- Evaluate different fitness functions
- Compare: Stepwise, GA and ACO algorithms against ground truth using identified fitness function

Model fitting done in nlmixr2

GA, Genetic Algorithm
ACO, Ant Colony Optimistion

Table of Contents

Methods: General workflow

Methods: Search Space

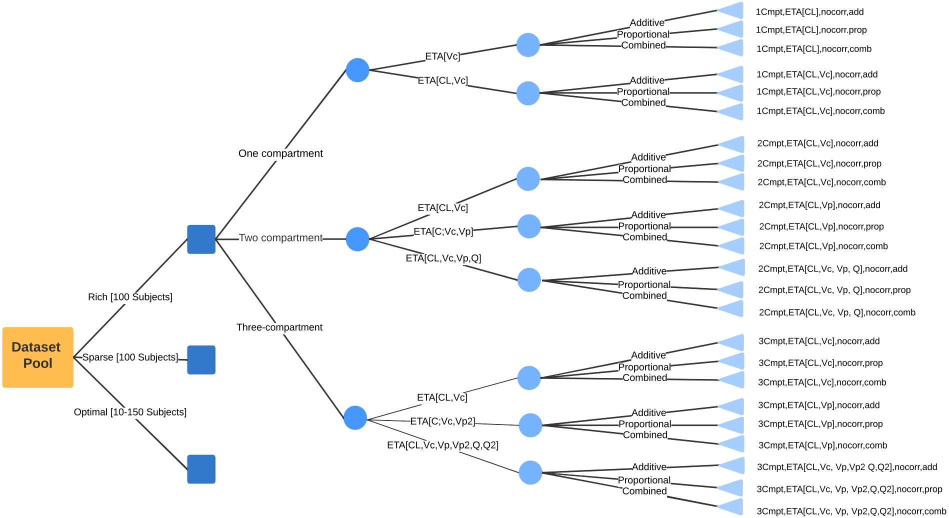
Model Components in the Search Space

Component No.	Description	Options
1	No. of compartments	1, 2, 3
2	Presence or not presence of IIV on Vc	0 (no), 1 (yes)
3	Presence or not presence of IIV on Vp	0 (no), 1 (yes)
4	Presence or not presence of IIV on Q	0 (no), 1 (yes)
5	Presence or not presence of IIV on Vp2	0 (no), 1 (yes)
6	Presence or not presence of IIV on Q2	0 (no), 1 (yes)
7	Presence or not presence of correlation	0 (no), 1 (yes)
8	Residual unexplained Model (RUV)	additive, proportional, combined

Vc, central volume of distribution
Vp, first peripheral volume of distribution
Q, inter-compartmental clearance for the first peripheral compartment
Vp2, second peripheral volume of distribution
Q2, inter-compartmental clearance for the second peripheral compartment

Methods: General workflow

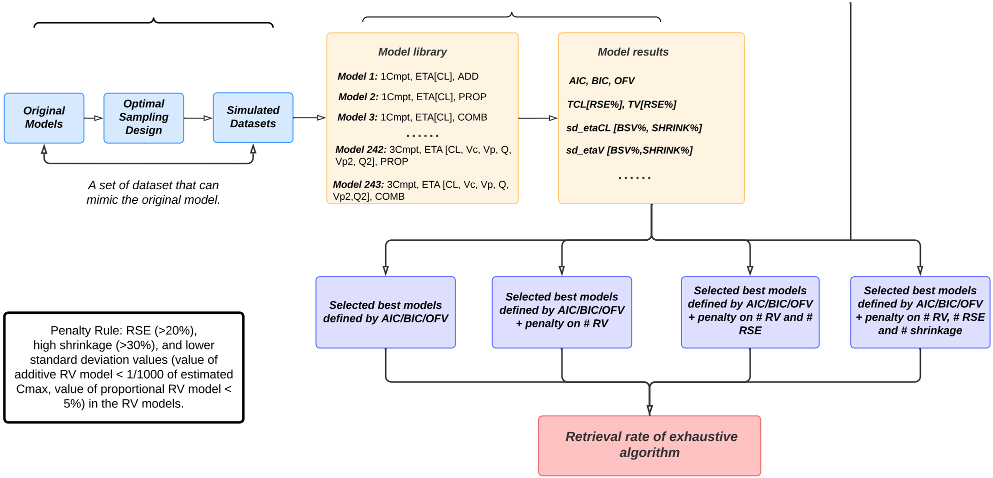
Methods: Characteristics of 72 Simulated Cases



Methods: General workflow

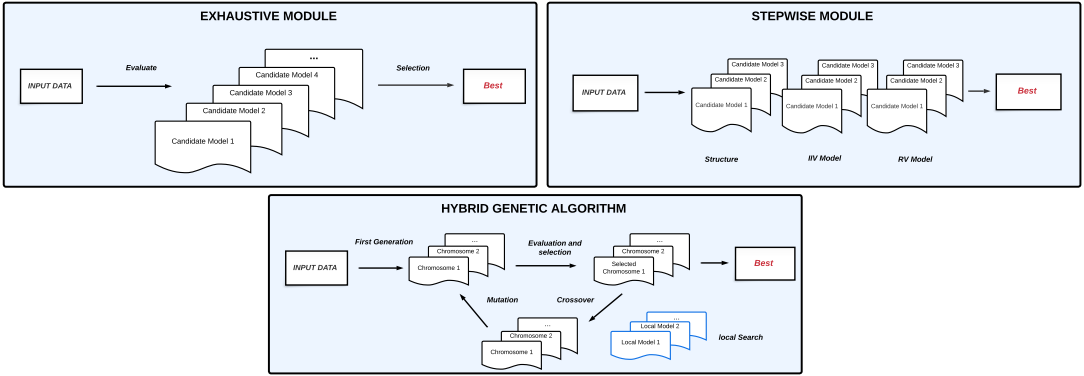
Methods: Fitness Function Exploration

Step 1: Generation of simulated datasets **Step 2: Parameter Estimation** **Step 3: Criteria evaluation**



Methods: General workflow

Methods: General Workflow of Designed Algorithms

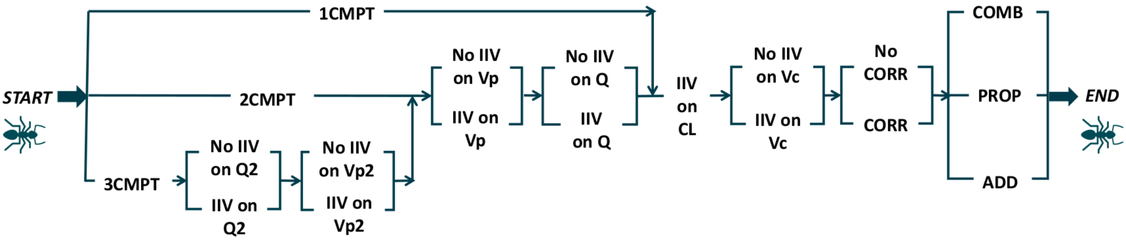


ALGORITHM DESIGN:

ACO in PopPK modelling

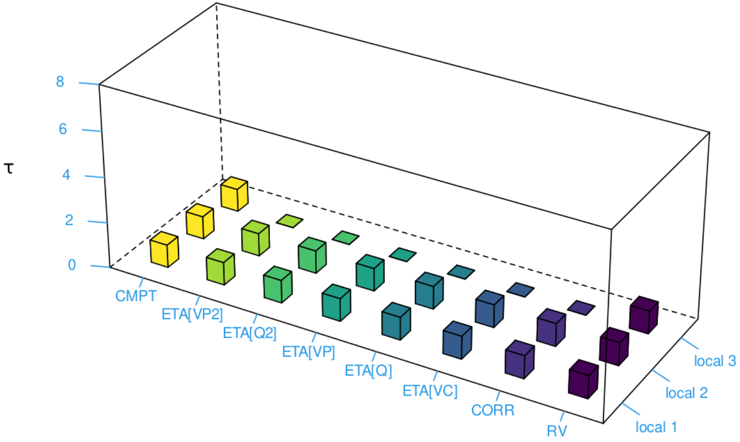
Methods: ACO design in PopPK modelling

Step 1. Solution Construction



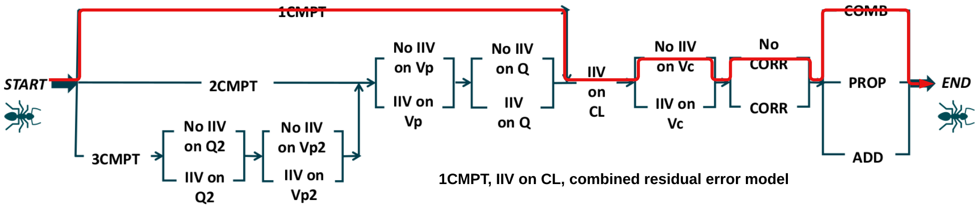
Methods: ACO design in PopPK modelling

Step 2. Pheromone initialisation

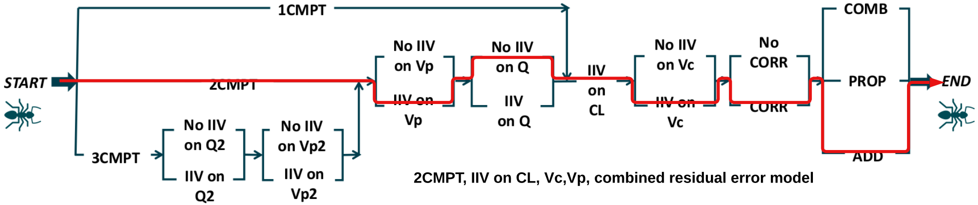


Methods: ACO design in PopPK modelling

Step 3. Ant Practice



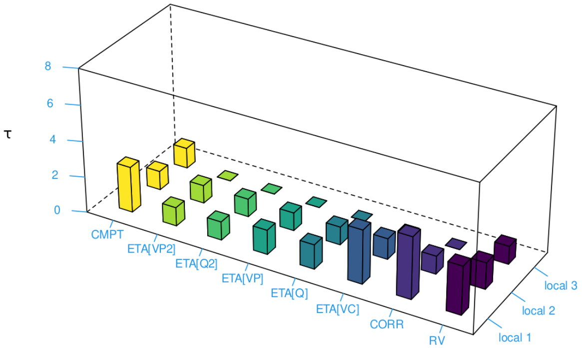
1CMPT, IIV on CL, combined residual error model



2CMPT, IIV on CL, Vc,Vp, combined residual error model

Methods: ACO design in PopPK modelling

Step 4. Pheromone generation and evaporation

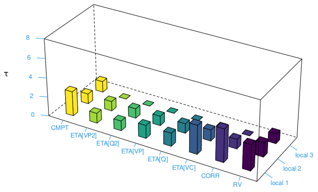


Pheromone generation $\Delta\tau = \frac{1}{Rank(fitness)}$

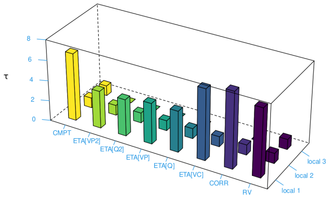
After pheromone evaporation $\tau = (1-\rho)\tau_0 + \Delta\tau$

Methods: ACO design in PopPK modelling

Step 5. Start new travel and repeat the process

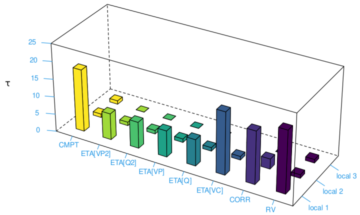


Travel 1



Travel 2

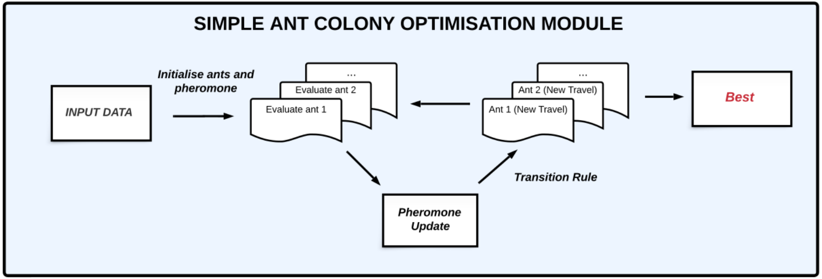
...



Travel 15

The probability of each node/local path was calculated based on the ratio of the pheromone deposited on that each node/local path to the total pheromone present in all nodes for the corresponding group.

Methods: ACO design in PopPK modelling

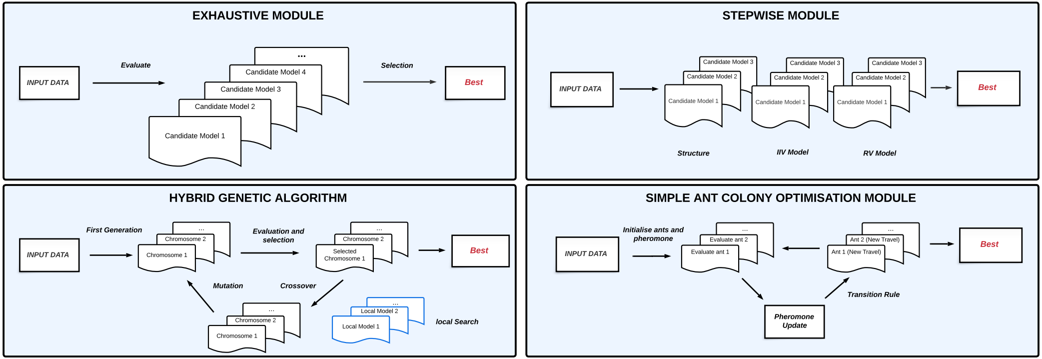


- Initialisation
- Parameter estimation and model evaluation
- Pheromone update for the next travel

Methods: General workflow

Methods: General Workflow of Designed Algorithms

Performance evaluation

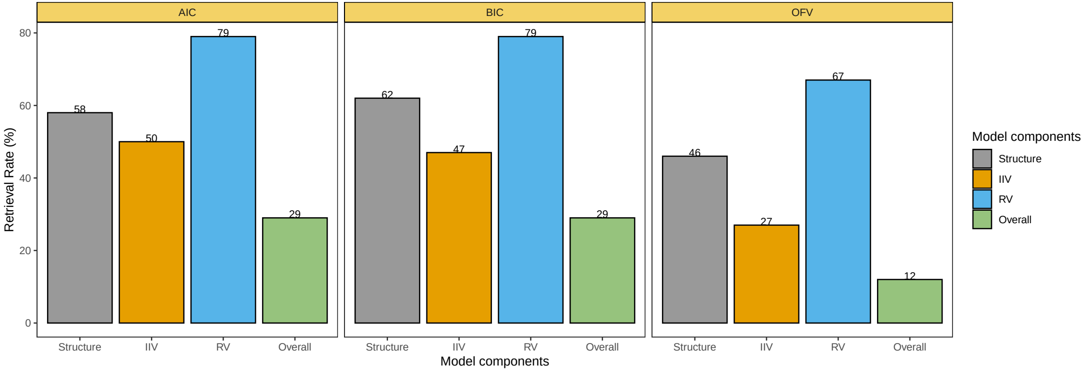


Accuracy rate, percentage of models selected by the test algorithms that matched the "true best models" identified by exhaustive algorithm for 72 cases.

Table of Contents

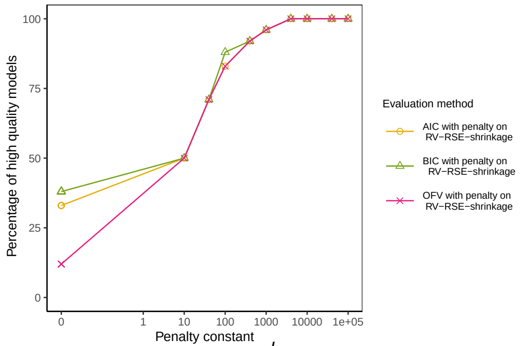
Results: Fitness Function

Retrieval rate of simulated models by exhaustive algorithm using only AIC, BIC and OFV

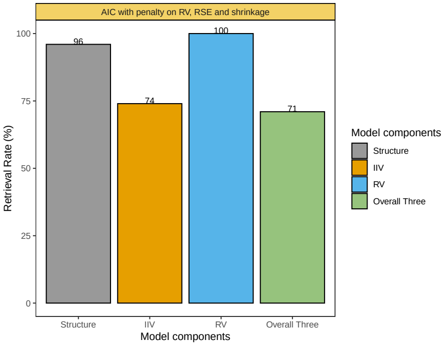


Results: Fitness Function

Percentages of high quality models selected by exhaustive algorithm



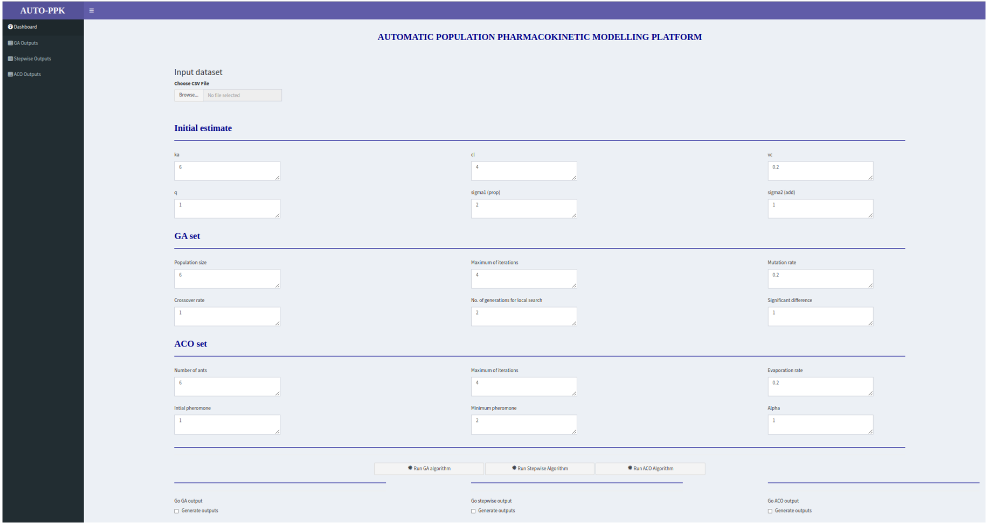
Retrieval rate of simulated models by exhaustive algorithm using the fitness function



$$fitness = AIC + \sum_{i=1}^{k} 10000\mathbb{1}_{RSE>20\%} + 10000\mathbb{1}_{Shrinkage>30\%} + 10000\mathbb{1}_{\sigma 1<1,\sigma 2<0.05}$$

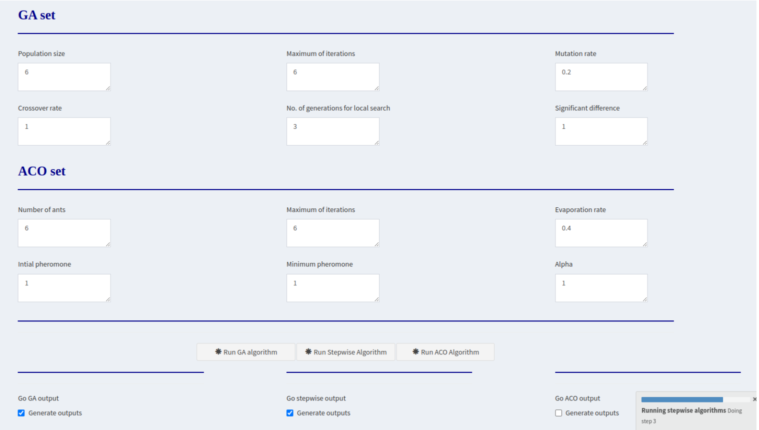
ALGORITHMS: APP DEMO

Results: R Shiny App Interface



Results: R Shiny App Interface

Case 1. 1Cmpt, IIV on CL, additive residual error model (Sparse data)



Results: R Shiny App Interface

Case 1. 1Cmpt, IIV on CL, additive residual error model (Sparse data)

AUTO-PPK

- Dashboard
- GA Outputs
- Stepwise Outputs
- ACO Outputs

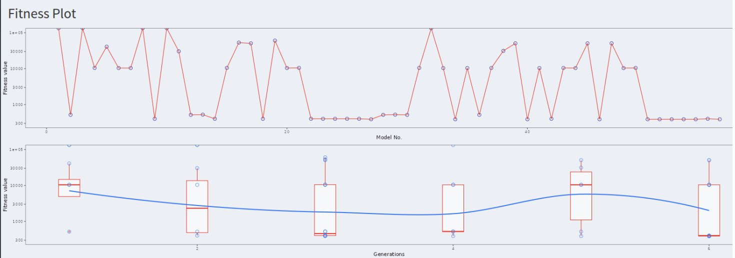
Model Development Summary

Run.no.	Iteration.No.	Iteration.Description	Model.Description	AIC	Fitness.Value
1	1	Compartment model	1Cmpt,IIV.cl,nocorr,combined	402.11	402.11
2	1	Compartment model	2Cmpt,IIV.cl,nocorr,combined	408.39	10408.39
3	1	Compartment model	3Cmpt,IIV.cl,nocorr,combined	498.67	60498.67
4	2	IIV model	1Cmpt,IIV.cl,nocorr,combined	402.11	402.11
5	2	IIV model	1Cmpt,IIV.cl.vc,nocorr,combined	532.31	10532.31
6	2	IIV model	1Cmpt,IIV.cl,nocorr,combined	402.11	402.11
7	3	Correlation model	1Cmpt,IIV.cl,nocorr,combined	402.11	402.11
8	3	Correlation model	1Cmpt,IIV.cl,corr,combined	402.11	402.11
9	4	RV model	1Cmpt,IIV.cl,nocorr,additive	389.88	389.88
10	4	RV model	1Cmpt,IIV.cl,nocorr,proportional	518.06	518.06

Results: R Shiny App Interface

Genetic Algorithm Output

Dashboard
GA Outputs
Stepwise Outputs
ACO Outputs

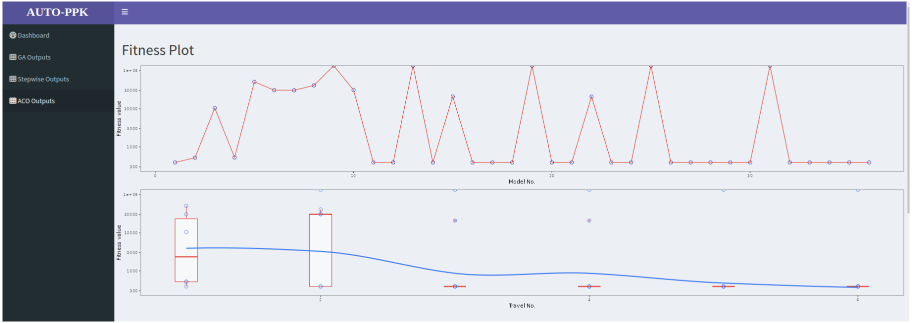


Show 25 entries Search:

i	AIC	BIC	OBJFV	ll	npar	cmpt.iv1	cmpt.iv2	eta.vc	eta.vp	eta.vp2	eta.q	eta.q2	mcorr	rv1	rv2	AIC.RV.RSE.SHRIN
1						0	1	1	0	0	0	0	1	0	1	
2	518.0605	525.7086	418.1667	-255.0303	4	0	1	0	0	0	0	0	0	1	0	518.0605
3						1	1	1	1	1	0	0	0	0	1	
4	471.7709	481.331	369.8771	-230.8855	5	0	1	1	0	0	0	0	0	0	1	10471.7709
5	909.1715	924.4677	801.2776	-446.5857	8	1	0	0	1	0	1	0	0	0	1	40909.1715
6	408.393	421.7772	302.4991	-197.1965	7	1	0	0	0	0	0	0	0	1	1	10408.393
7	408.393	421.7772	302.4991	-197.1965	7	1	0	0	0	0	0	0	0	1	1	10408.393

Results: R Shiny App Interface

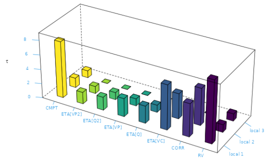
ACO Algorithm Output



Results: R Shiny App Interface

ACO Algorithm Output

Pheromone Plot



Show 25 entries Search:

i	AIC	BIC	OBJFV	ll	npar	cmpt.iv	eta.vc	eta.vp	eta.vp2	eta.q	eta.q2	mcorr	rv	AIC.RSE.SHRINK
1	389.877	397.5251	289.9831	-190.9385	4	1	0	0	0	0	0	0	1	389.877
2	518.0605	525.7086	418.1667	-255.0303	4	1	0	0	0	0	0	0	2	518.0605
3	398.8801	410.3522	294.9862	-193.44	6	2	0	0	0	0	0	0	1	10398.8801
4	525.2227	536.6948	421.3288	-256.6113	6	2	0	0	0	0	0	0	2	525.2227
5	671.4269	686.7231	563.5331	-327.7135	8	3	0	0	0	0	0	0	1	50671.4269
6	536.7686	552.0648	428.8748	-260.3843	8	3	0	0	0	0	0	0	2	30536.7686
7	415.801	429.1851	309.9071	-200.9005	7	2	0	0	0	1	0	0	1	30415.801
8	721.2218	742.254	607.3279	-349.6109	11	3	1	0	1	1	0	0	2	40721.2218

Results: GA and ACO Final Parameter setting

GA parameters

- Population size: 10
- Crossover probability: 1
- Mutation rate: 0.2
- Maximum of iterations: 15

ACO parameters

- Ant size : 10
- Evaporation rate: 0.4
- Alpha value: 1
- Maximum of iterations: 15

Results: Algorithm Performance

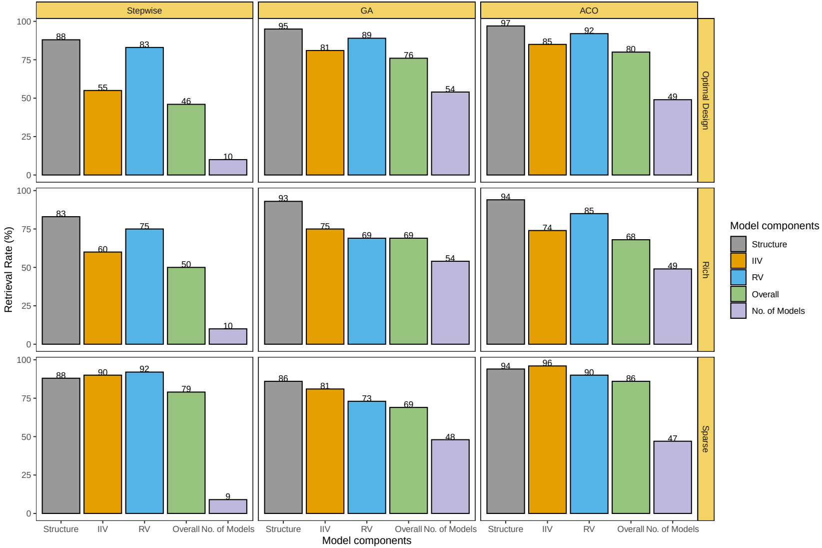


Table of Contents

Conclusion

Fitness Function

- Consider RSE and shrinkage, variance of RV model
- 10000 penalty was appropriate
- May need to revise when extending to other model/data types

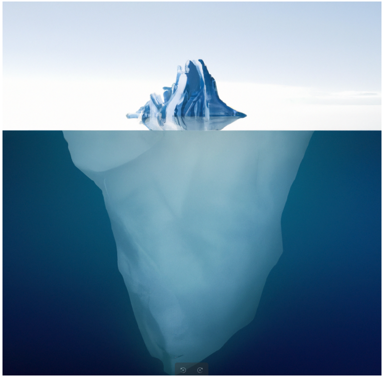
Algorithm Performance

- Optimal design data: ACO and GA similar, both outperform stepwise
- Rich data: ACO and GA similar, both outperform stepwise
- **Sparse data: ACO superior to GA and stepwise, stepwise better than GA**

Future Work

Considerations in the future

- Oral/other routes of administration
- Nonlinear kinetics
- Setting initial estimates
- Application to Real-World Data
- Publish as R-package



Acknowledgements

Funder:

- Clinical Informatics Research Programme
- John Lipscombe Memorial Travel Awards

NHS Great Ormond Street Hospital for Children DRIVE DATA RESEARCH, INNOVATION, AND VIRTUAL ENVIRONMENTS

People:

- Prof Joseph Standing
- Dr. Frank Kloprogge

PKPD AI

Thank you for your attention!

Questions & Answers