Genetic Algorithms and Their Applications in PK/PD Data Analysis

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Introduction

Drug discovery and development demands versatile and efficient prediction and optimisation tools which can effectively handle complex and multi-variant problems (van de Waterbeemd *et al.*, 2003). Currently, almost all of the data analysis and optimisation software used in PK/PD studies are based on either gradient-based (e.g. Gauss-Newton and Newton-Raphson) or direct/random search (e.g. Nelder-Mead) optimisation methods. However, these methods cannot effectively tackle such complex problems.

Recently, evolutionary optimisation algorithms have been developed and Genetic Algorithms (GAs) are amongst the most popular algorithms. The latter have not been used in PK/PD data analysis. The aim of this study was to demonstrate that GAs can be used as alternatives to conventional methods in PK/PD data analysis.

Genetic Algorithms Principles

GAs mimic natural selection (Goldberg, 1989) and have been applied successfully in various fields, including chemistry, biology, and many engineering disciplines. They are based on Darwin's theory of evolution whose principles can be summarised as follows:

- Personality of parents is passed onto offspring during reproduction;
- Fittest individuals are liable to have more offspring and thus drive the population towards their favourable characters;
- Offspring's traits are partly inherited from their parents and partly generated through mutation.

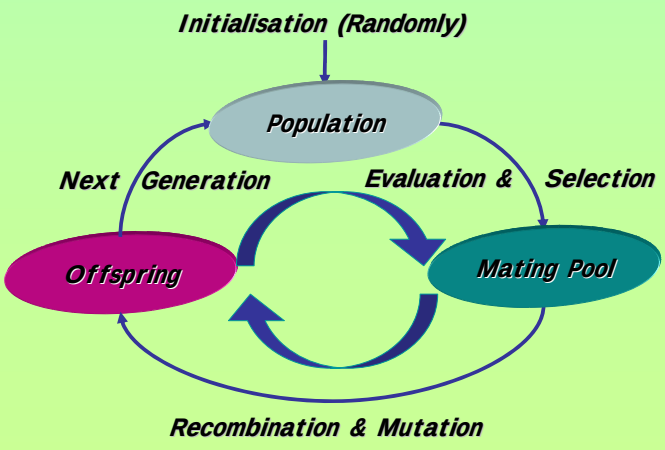
The following figure represents the relationship between an optimisation problem and the evolution of a population.

• **Optimisation Problem**	⟷	• **Evolution of a Population**
• The problem	⟷	• The environment
• A potential solution	⟷	• An individual in the population
• Decision parameters	⟷	• Traits
• Superiority	⟷	• Fitness

Superiority: How good (based on the objective function) is a solution in comparison with others

Fitness: Chances for survival to the next generation and reproduction

Generally, there are three main steps in a GA, namely: fitness evaluation of the individuals in the population, selection of parents for mating and recombination of offspring to survive to the next generation. This process of evolution continues until predefined criteria are met. A schematic diagram of GA is shown below.



Case Studies

In order to assess the performance of GA in PK/PD studies, we applied GAs to different problems including:

- PK/PD Fitting;
- Mechanism-Based Inhibition (MBI) Parameter Estimation;
- Physiologically-Based Pharmacokinetic (PBPK) Modelling.

In the following case, the performance of GA was compared with that of WinNonLin in a PK fitting problem.

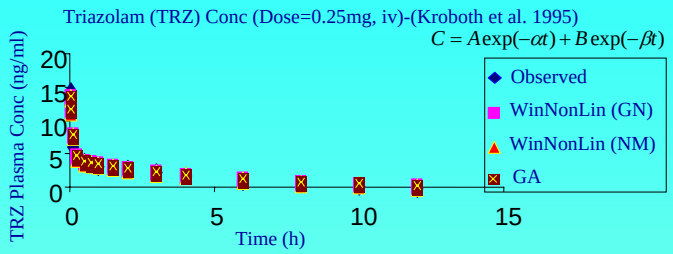


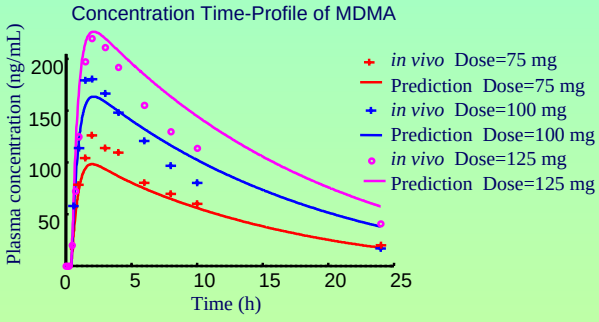
Table 1 – A comparison between GA and WinNonLin in PK fitting.

Optimisation Method	A	B	α	β	Obj*	Remarks
WinNonLin (Gauss-Newton)	11.89	4.39	11.85	0.198	14.70	2 Iterations
WinNonLin (Nelder-Mead)	11.87	4.38	11.86	0.195	14.70	44 Trials
GA	11.89	4.39	11.84	0.197	14.70	70 Trials

* The objective function values.

GA was also applied to determine the MBI kinetic values of 81 virtual MBIs with known starting values. GA successfully predicted the kinetic values and the bias did not exceed 20% in any of the cases. However, the conventional experimental protocol introduced more than 100% bias for at least one of the kinetic parameters of 15 of the virtual MBIs (Yang *et al*, submitted).

In order to simulate the *in vivo* kinetic consequences of MBI of CYP2D6 by Ecstasy a model with physiologically-based components of drug metabolism was developed. Based on the *in vitro* information, plasma concentration-time profiles of MDMA after various doses were successfully simulated and compared with reported observations. (Yang *et al*, submitted).



Conclusions

Using different case studies, we have shown that GAs are plausible alternatives to conventional optimisation methods. GAs have shown superior performances in multi-modal and multi-variant optimisation problems. However, they should not be used where the conventional optimisation methods are efficient enough. The use of GA in other PK/PD problems warrants further investigation.

References

Goldberg, D.E. (1989), Wokingham: Addison Wesley.
Kroboth, P.D., *et al*. (1995), *J Clin Psychopharmacol*, 15, 259-62.
van de Waterbeemd, H. & Gifford, E. (2003), *Nature Reviews Drug Discovery*, 2, 192-204.