Optimization of Compartment Models by Using Metaheuristic Approaches

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Motivation

Problem

Parameter estimation of compartment models

Goal

Parameter estimation without linearization of the response function

Method

Metaheuristic methods - Genetic Algorithm (GA)

Compartment Model

- Modeling of dynamical systems plays a very important role in applied science.

- Compartment models are among the most important tools used for analyzing dynamical systems.

- Compartment models are often used to describe transport of material in biological systems. These are widely used in many fields of science and engineering, e.g. bio-chemistry, physiology, radioactive isotopes, and pharmacokinetics.

Compartment Model

- A pharmacokinetic model explains how the concentration of a drug in blood plasma declines over time.
- This model can be shown as a compartmental diagram which helps clarify what is going on.

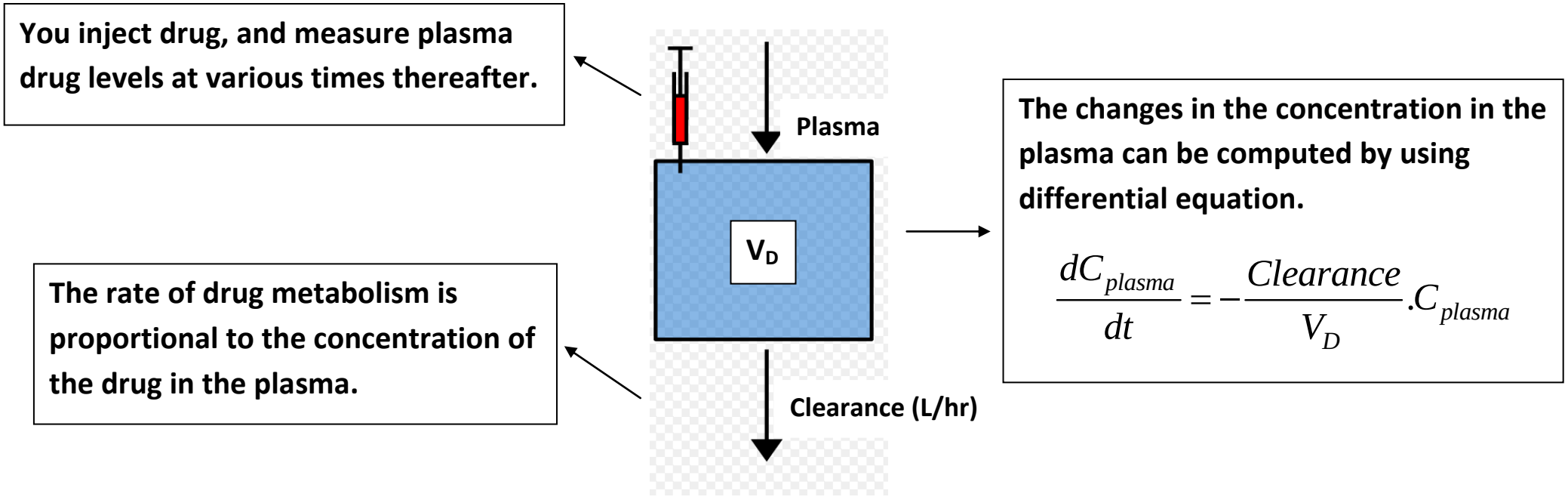


Figure 1. A compartmental diagram

Polyexponential Form

- Under certain assumptions, integration of differential equation leads to be polyexponential form as

$$C_p = \sum_{j=1}^{k} \alpha_j e^{-\lambda_j t} \qquad (1)$$

Concentration at time *t*

***j*th coefficient (may be positive/negative)**

Exponent of the *j*th exponential term

- The Eq.(1) express the response as a polyexponential function of time *t*.

Stripping (Back-projection) Method

- In order to obtain the estimates of coefficients and exponents, an operation called "stripping or back projection" is used for pharmacokinetic studies.

- For stripping method, straight lines are drawn through sets of data points "by sight", and these lines are extrapolated back to the ordinate scale on semilogarithmic graph.

Stripping (Back-projection) Method

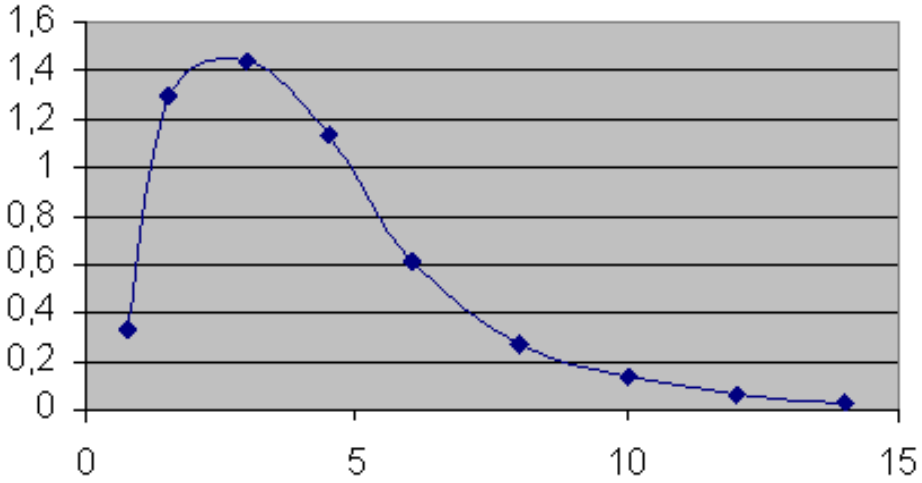


Figure 2.a The original graph for C-t

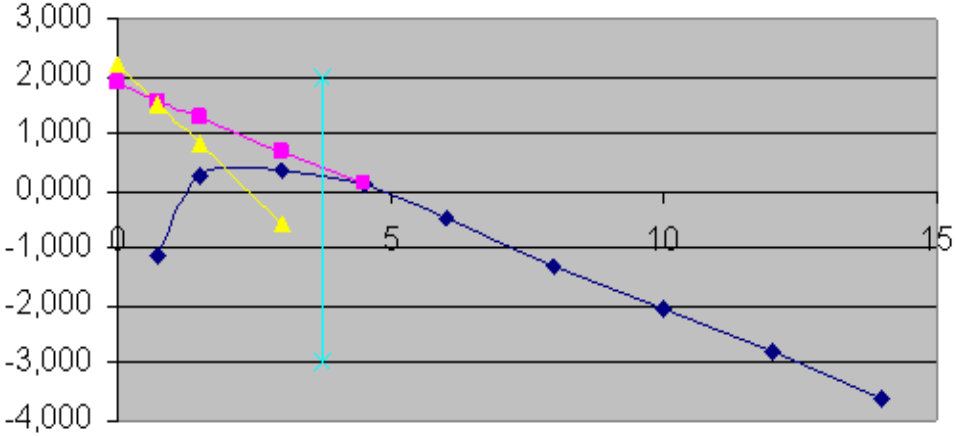


Figure 2.b The semilogarithmic graph for C-t

The major problem with performing the method this way is that each person who applies the method to the same data set will usually obtain a different answer than the next person.

Polyexponential Regression Model

- The statistical problems in the present context are basically those of parameter estimation for polyexponential regression model.

$$Y_i = \beta + \sum_{j=1}^{k} \alpha_j e^{-\lambda_j t_i} + \varepsilon_i \quad , \quad i = 1, 2, \ldots, n \qquad (2)$$

Observed response

Constant
(assumed to be 0)

Random errors
(assumed to be independent random variables with zero mean)

Objective Function

$$\phi(\boldsymbol{\theta}) = \sum_{i=1}^{n}\left(Y_i - \hat{Y}_i\right)^2 = \sum_{i=1}^{n}\varepsilon_i^2 \qquad (3)$$

$$\left[\alpha_1\ \alpha_2 \ldots \alpha_k ; \lambda_1\ \lambda_2 \ldots \lambda_k\right]$$

$$\sum_{j=1}^{k}\hat{\alpha}_j e^{-\hat{\lambda}_j t_i}$$

- It is clear that the objective function has nonlinearity in parameters.
- In this case derivative free methods should be more proper rather than derivative based methods for Eq.(3).

Metaheuristic Methods

- Metaheuristics are the general class of stochastic optimization methods which employ some degree of randomness to find optimal solutions for hard problems.

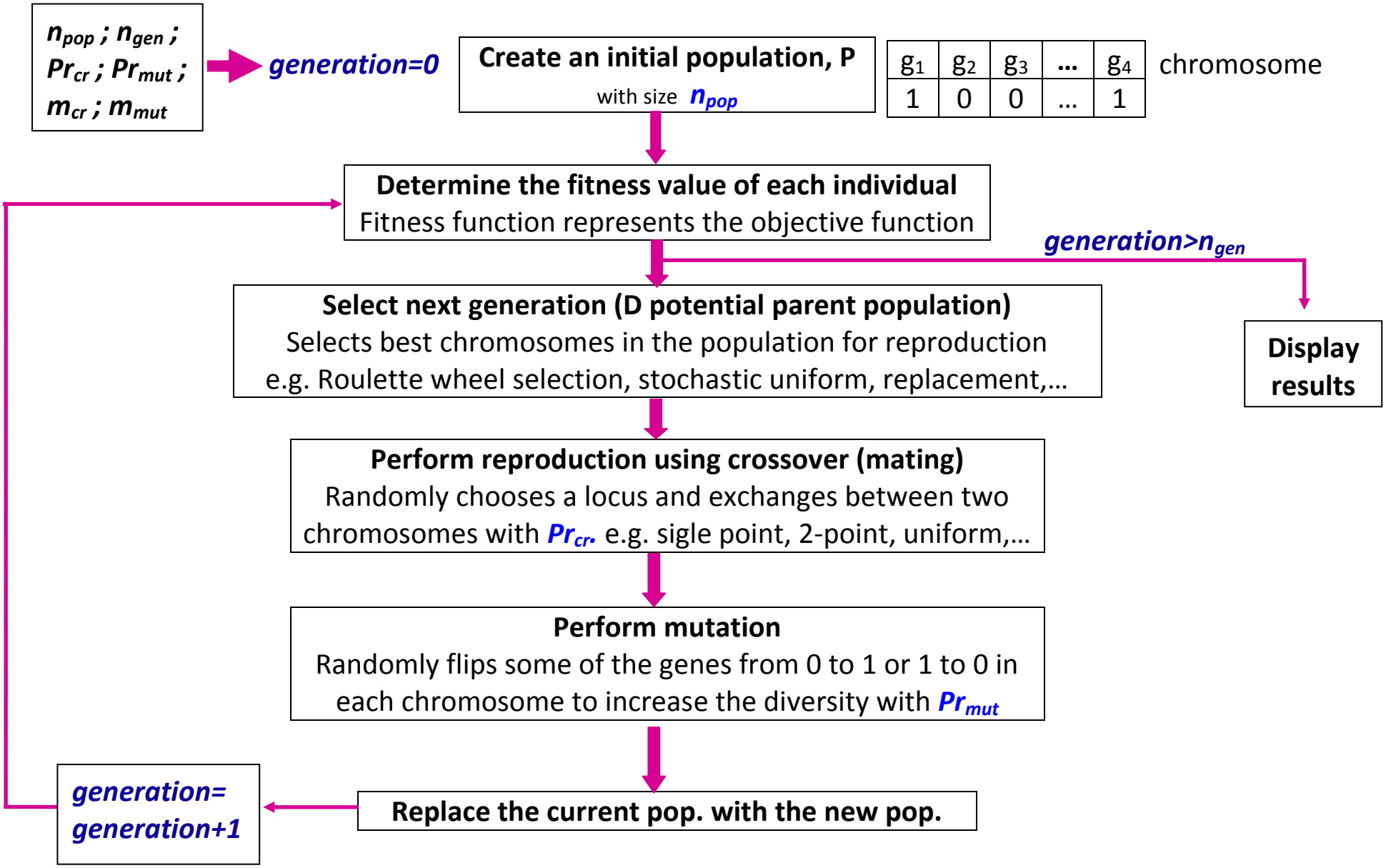
- Genetic Algorithm (GA) is a metaheuristic method based on natural selection and genetic mechanism.

- The basic principle of it is the Darwinion "survival of the fittest" approach.

Genetic Algorithm

- GAs are intelligent exploitation of random search used in many NP hard, complex, and nonlinear problems.
- GAs search from a population points, not a single point.
- GAs use objective function information, not derivatives.
- GAs use probabilistic transition rules, not deterministic rules.
- GAs can produce the solution without requiring initial solutions by searching from many search points simultaneously.

How does the GA work for parameter estimation?



Application: (One-compartment model)

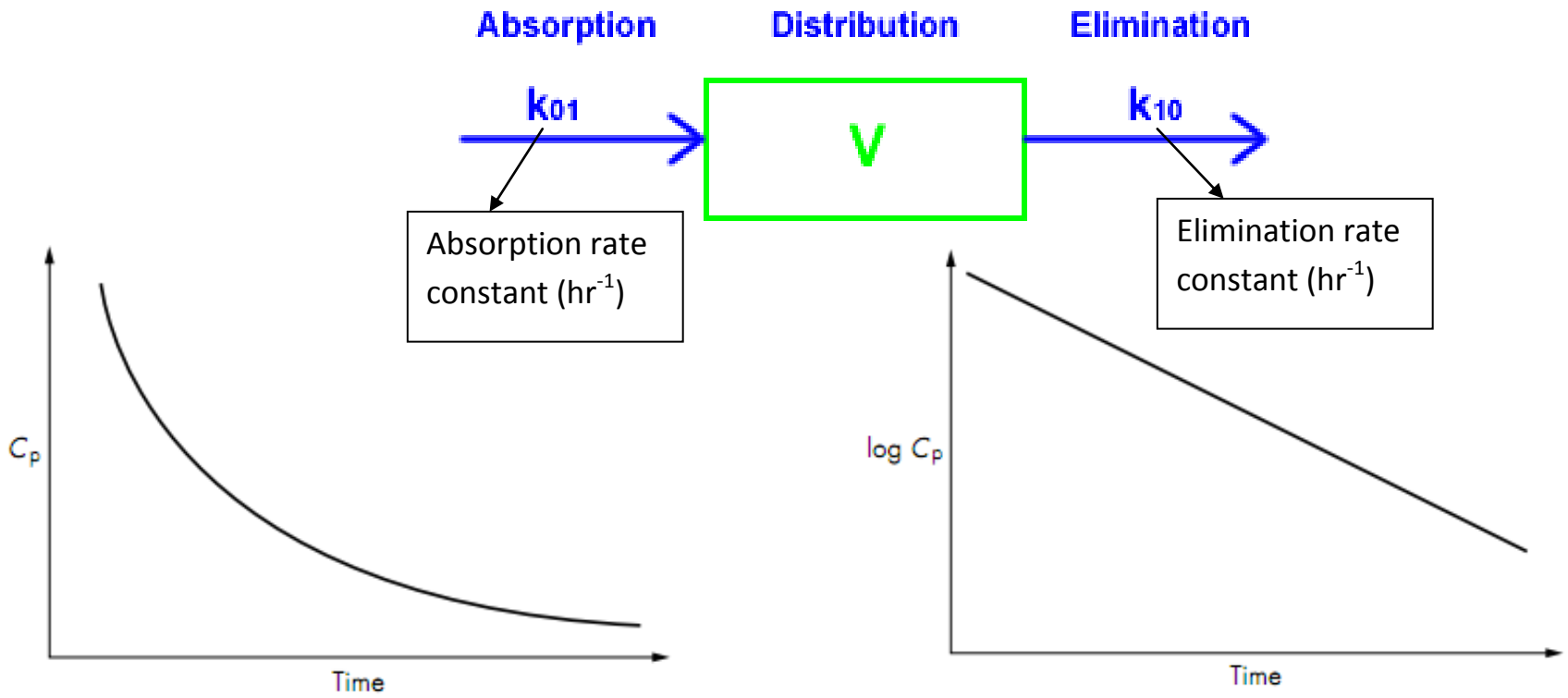


Figure 3. Plasma concentrations for one-compartment model

$$C_p = \alpha_1 e^{-\lambda_1 t} + \alpha_2 e^{-\lambda_2 t}$$

$$\lambda_1 = k_{10}$$

$$\lambda_2 = k_{01}$$

Data Set:

Observed plasma concentrations for 500 mg erythromycin

$t\,(hr)$:	0.75, 1.5, 3, 4.5, 6, 8, 10, 12, 14
$C_p\,(mg/ml)$:	0.33, 1.3, 1.44, 1.14, 0.61, 0.27, 0.13, 0.062, 0.026

- Estimate the pharmacokinetic parameters?

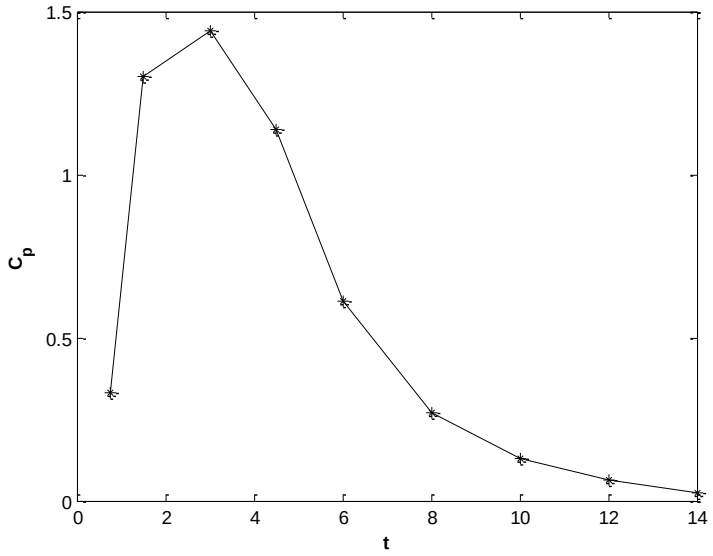


Figure 4. The original graph for C_p-t

Model:

$$Y_i = \alpha_1 e^{-\lambda_1 t_i} + \alpha_2 e^{-\lambda_2 t_i} + \varepsilon_i, \qquad i = 1, 2, \ldots, 9$$

Objective Function:

$$\phi(\boldsymbol{\theta}) = \sum_{i=1}^{9} \left[Y_i - \left(\alpha_1 e^{-\lambda_1 t_i} + \alpha_2 e^{-\lambda_2 t_i} \right) \right]^2$$

Parameters for GA:

$n_{pop} = 100;\ n_{gen} = 200$

$\Pr_{cr} = 0.90\ ;\ \Pr_{mut} = 0.01;\ m_{cr} = 20;\ m_{mut} = 20$

Roulette Wheel Selection

Single Point Crossover

Bit flip mutation

Interval of Parameters:

	α_1	λ_1	α_2	λ_2
Lower bound:	5	0	-10	0
Upper bound:	8	1	-8	1

Parameter Estimates:

	α_1	λ_1	α_2	λ_2	MSE
Stripping	6.51	0.392	-9.14	0.926	0.0315
GA	6.8456 (0.6994)	0.3708 (0.0165)	-8.9305 (0.6239)	0.8206 (0.0892)	**0.0195**

Application: (Two-compartment model)

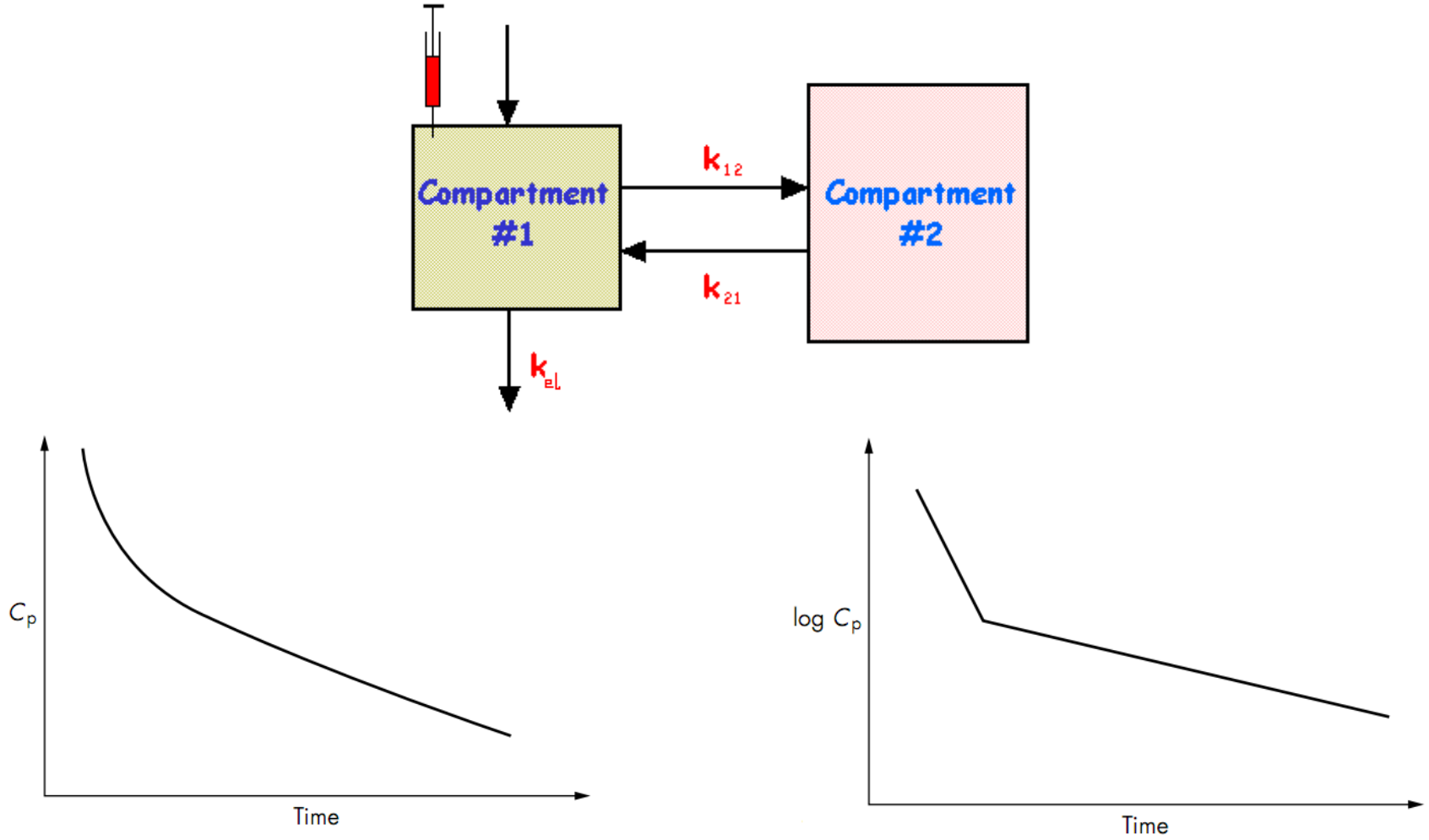


Figure 5. Plasma concentrations for two-compartment model

$$C_p = \alpha_1 e^{-\lambda_1 t} + \alpha_2 e^{-\lambda_2 t}$$

$$k_{21} = \frac{\alpha_1 \lambda_2 + \alpha_2 \lambda_1}{\alpha_1 + \alpha_2} \qquad k_{el} = \frac{\lambda_1 \lambda_2}{k_{21}} \qquad k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{el}$$

Data Set:

Observed plasma concentrations for 75 mg I.V.

$t\,(hr)$:	0, 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, 24
$C_p\,(mg/ml)$:	16.4, 14.2, 12.53, 11.17, 10.09, 7.56, 6.44, 5.85, 5.16, 4.65, 3.18, 3.12, 2.09

- Estimate the pharmacokinetic parameters?

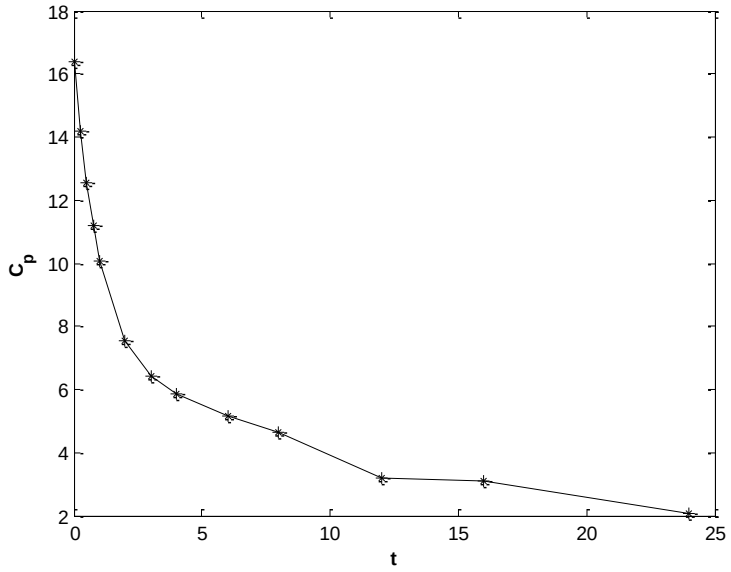


Figure 6. The original graph for C_p-t

Model:

$$Y_i = \alpha_1 e^{-\lambda_1 t_i} + \alpha_2 e^{-\lambda_2 t_i} + \varepsilon_i, \qquad i = 1, 2, ..., 13$$

Objective Function:

$$\phi(\boldsymbol{\theta}) = \sum_{i=1}^{13} \left[Y_i - \left(\alpha_1 e^{-\lambda_1 t_i} + \alpha_2 e^{-\lambda_2 t_i} \right) \right]^2$$

Interval of Parameters:

	α_1	λ_1	α_2	λ_2
Lower bound:	9	0	6.5	0
Upper bound:	10	1.5	7.5	1

Parameter Estimates:

	α_1	λ_1	α_2	λ_2	k_{12}	k_{21}	k_{el}	MSE
Stripping	9.59	1.06	7.05	0.0509	0.5197	0.4784	0.1128	0.5066
GA	9.4381 (0.2216)	0.9876 (0.0442)	6.946 (0.2449)	0.053 (0.0035)	0.4749	0.4492	0.1165	**0.3102**

Conclusions

- ✓ Compartment models are considered as nonlinear response problems.
- ✓ Basic definitions about them, related to the pharmacokinetic studies, are given.
- ✓ The compartment models are represented as polyexponential regression models in the statistical context.
- ✓ Stripping (back-projection) method, a well used method in the literature for parameter estimation, is explained.
- ✓ Basic definitions and working principle about GA are given.
- ✓ The GA is applied one and two compartment models for parameter estimation.
- ✓ It is seen from the results that GA gives smaller MSE value than stripping method.

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