A GENETIC ALGORITHM FOR CURVE FITTING: A POSSIBLE CHOICE FOR UNSATISFACTORY NONLINEAR REGRESSIONS

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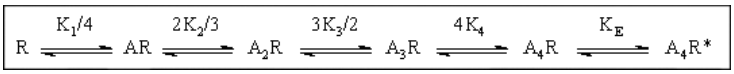
The Hill equation is likely the most used model for curve-fitting in pharmacological research (Christopoulos and Lew, 2001). However, it presents a possible drawback as it cannot account for asymmetric concentration-effect curves (Giraldo *et al*., 2002). The Richards function solves this problem by including an additional parameter (s). Hill and Richards models are nested, being the Hill function a particular case of Richards equation if the s parameter is equal to one. A value of s different from one allows a theoretical curve to display an asymmetric shape. Regretfully, it has been found that, in a number of cases, the Richards function performs deficiently in curve fitting if gradient nonlinear regression is used (Van Der Graaf and Schoemaker, 1999). The reason for that may lay in the strong correlation found between some of the parameters of the Richards model. This correlation can affect the location, slope, and symmetry parameters yielding nonsensical values, very large errors or even failing to converge. A genetic algorithm (GA) can be a useful methodology to the determination of the parameters of difficult fitting problems (Maeder *et al*., 2004). In particular, this technique avoids the sensitivity of local optima to the initial estimates supplied to the nonlinear regression procedure.This study presents a GA approach for the estimation of function parameters, in particular Richards function parameters. To test the performance of our algorithm the four binding sites ligand-gated ion channel (Equation 1) is selected as a case study.



where K1, …, K4 are the microscopic equilibrium dissociation constants

$$K_E = \frac{[A_4R^*]}{[A_4R]}$$

and is the equilibrium constant for the opening reaction. If we define the effect as the proportion of receptors in the open state, Equation 2 is obtained:

$$E = \frac{[A]^4 K_E}{K_1K_2K_3K_4 + 4K_2K_3K_4[A] + 6K_3K_4[A]^2 + 4K_4[A]^3 + [A]^4(1+K_E)}$$

It can be shown (Giraldo, 2003) that Equation 2 tends to a Richards function in the case of very low efficacy (KE << 1) and absence of co-operativity (Ki = K for each binding step). In the cases tested (Ki=10-6, and KE either equal to 1 or equal to 10-5), our GA provided similar or better estimates than the nonlinear regression method when the latter performed well or badly, respectively. Because the assessment of asymmetry may be important both for accurate estimation of empirical pharmacological parameters and for the mechanistic analysis of those biological systems where asymmetry is an intrinsic and relevant feature, our approach could be a possible choice in those situations in which gradient nonlinear regression (in particular of Richards function) is unsatisfactory.

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