Assessing agonist efficacy in an uncertain Em world

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The operational model of agonism

$$A + R \underset{}{\overset{K_A}{\rightleftharpoons}} AR \longrightarrow E$$

$$K_A = \frac{[A][R]}{[AR]}$$

The Transducer Function

$$E = \frac{E_m [AR]^n}{K_E^n + [AR]^n}$$

E_m → Maximum effect of the system

K_E → Intrinsic efficacy

$$E = \frac{E_m \tau^n [A]^n}{(K_A + [A])^n + \tau^n [A]^n}$$

$$\tau = \frac{[R_0]}{K_E}$$ **Operational Efficacy**

$$[R_0] = [R] + [AR]$$

Asymptote Parameter

$$\alpha = \lim_{[A]\to\infty} E \qquad \alpha = \frac{E_m \tau^n}{1 + \tau^n}$$

Location Parameter

$$[A_{50}] = [A]_{E=\frac{\alpha}{2}} \qquad [A_{50}] = \frac{K_A}{(2 + \tau^n)^{\frac{1}{n}} - 1}$$

Single or multiple Em for the same receptor?

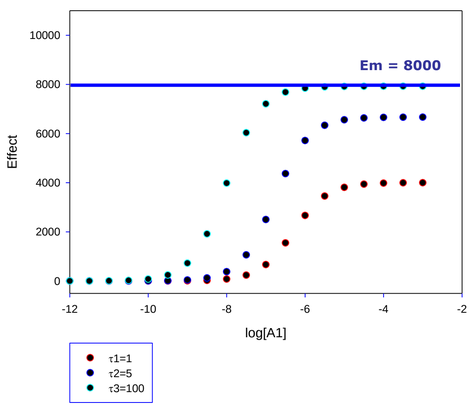
Theoretical ("true") parameter values: Em=8000, n=1, log(K_A)=-6, τ1=1, τ2=5, τ3=100

Initial values:

Em=6.000, n=2, log(K_A)=-4, τ1=5, τ2=15, τ3=50

Parameter estimates:

Em=8.000, n=1, log(K_A)=-6, τ1=1, τ2=5, τ3=100



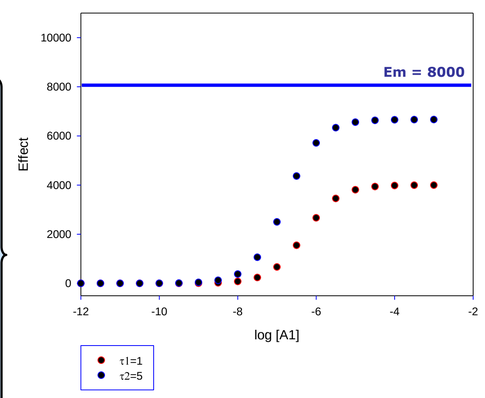
Full agonist A1

Initial values:

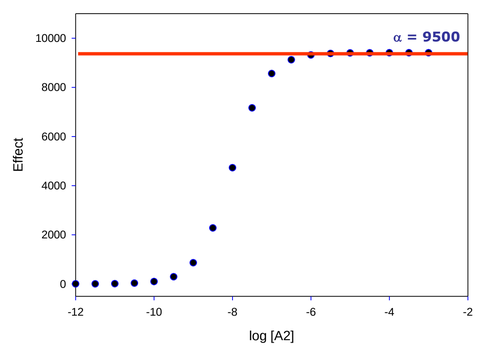
Em=6.000, n=2, log(K_A)=-4, τ1=5, τ2=15

Parameter estimates:

Em=8.000, n=1, log(K_A)=-6, τ1=1, τ2=5



Full agonist A1



Strong agonist A2

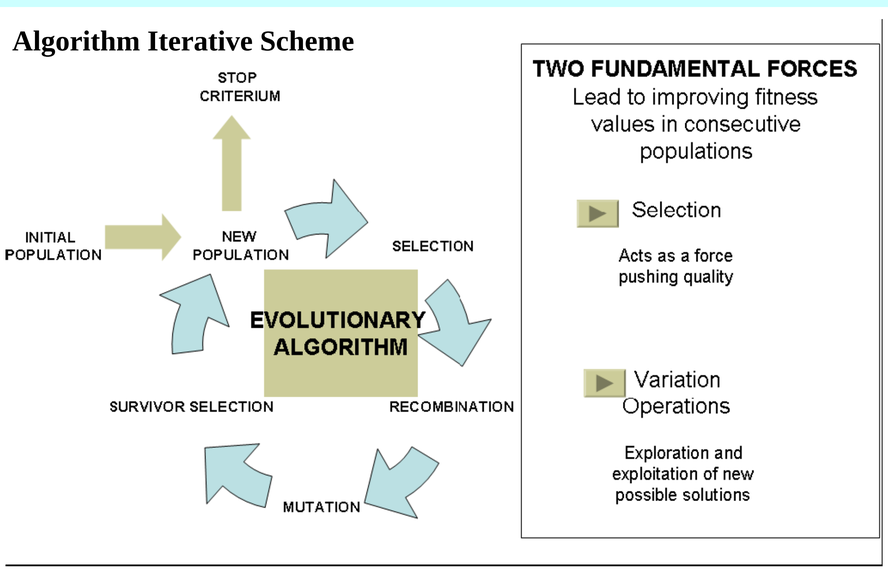
The operational model of agonism can find the "true" Em of the system

α > Em can be obtained from strong agonists or positive allosteric modulators

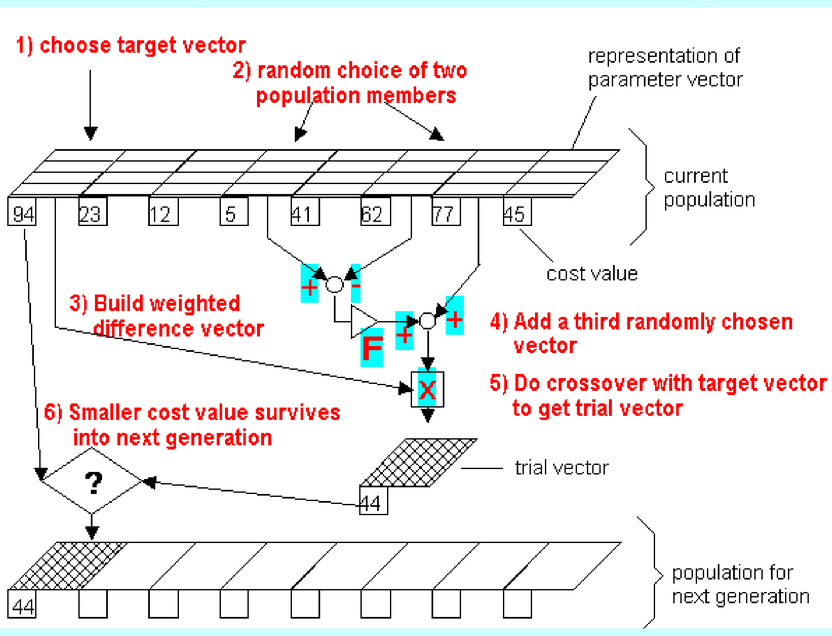
Hypothesis and Proposal

Strong agonists and positive allosteric modulators can produce top values greater than Em estimated from full agonists ⟹ **Either the estimated Em is not a true Em or there are multiple Em** ⟹ **Different Em values can arise from different active receptor conformations. An extension of the operational model of agonism is needed**

Methods. Differential Evolution (DE): An alternative technique for curve fitting



- DE is a very simple population-based, stochastic function minimizer
- DE is very powerful for solving real-valued, noisy, change over time, multimodal, nonlinear and non differentiable functions
- DE is suitable for particular pharmacologic cases where many parameters are included in the equations as, for instance, allosteism



References and Acknowledgements

(1) Black JW and Leff P (1983) Proc. R. Soc. Lond.B 220:141-162

(2) Leff P et al. (1990) J Pharmacol Methods 23(3):225-37

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