**Grid search and chaos synchronization as a tool to uniquely estimate parameters of a chaotic pharmacological system**

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**Objectives:** Many biological systems with feedback exhibit deterministic chaos. Current pharmacometric practice focuses on stochastic solutions based on Maximum Likelihood and Extended Least Squares metrics. Our research highlights some of the challenges in solving chaotic systems. We demonstrate that stochastic approaches are not necessarily robust for chaotic systems especially when the data are subject to experimental error and are sparsely sampled. We propose to estimate parameters based on a combination of chaos synchronization and coarse-to-fine grid search.

**Methods:** We demonstrate the sensitivity of chaotic systems to initial conditions and small perturbations of parameter values. We apply adaptive chaos synchronization according to Huang [1] in combination with coarse-to-fine grid search method to estimate and track the Dokoumetzidis cortisol model [2]. We compare the performance of the proposed method to that non-linear least squares regression approach.

**Results:** We evaluated data sets with and without substantial proportional and additive experimental error, with dense and sparse sampling schemes. The parameters converged to nominal values and the predictions tracked the system with high fidelity and without appreciable offset. Non-linear least squares regression was unable to estimate the parameters with high accuracy and yielded a substantial offset that increased with experimental error and sparsity of sampling.

**Conclusions:** The analysis supports the proposal that deterministic chaotic systems are well estimated using a deterministic approach and that a combination of chaos synchronization and grid search is highly effective.