436k Improved Parameter Estimation and Accuracy Using the Bootstrap Method

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In the past, new measurement technologies were developed to measure intracellular metabolites, mRNA and proteins - often referred to as ``omics" technologies. Parallel to this progression, the development of detailed mathematical models describing metabolic and signal transduction processes becomes very popular. However, knowledge on the dynamical behavior of cellular systems require the estimation of uncertain or even unknown kinetic parameters. Moreover, after estimation of the parameters, a statement on the precision of the parameters is required. A method frequently used in this field is the calculation of the Fisher-Information-Matrix (FIM) to describe the confidence region of the parameters. From a theoretical point of view, the application of the FIM is limited: (i) The FIM gives only lower bounds for the variance of a parameter, since the underlying model equations have nonlinear solutions. (ii) The resulting confidence region is symmetric with respect to the estimated parameters. In the study to be presented we overcome the mentioned problems by exploiting the so called bootstrap method (e.g. B. Efron, An Introduction to the Bootstrap, Chapman \& Hall, 1998). Briefly, like a Monte-Carlo Method the bootstrap uses stochastic elements and repeated simulation to analyze the properties of the system under consideration. A small biochemical network with 5 five parameters was modeled with a set of o.d.e.'s. to describe the temporal changes of the components. Experimental data were obtained by using a ``real" (in silico) model (different from the one that was used for the fit) with added noise. The bootstrap was applied by generating 500 new data sets that were fitted and the distribution of the parameters was analyzed by determining characteristic values (mean, median, variance) from the histograms. Results obtained with the bootstrap method were compared with results obtained with the FIM. We could show that, as expected, the prediction of the time course of important intracellular metabolites is improved very much by using the bootstrap. Implications for experimental design will also be discussed.