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**Cluster Approximation method for Inverse Problems:  
application to Model Parameter Estimation**

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We describe a new method for inverse problems that proceeds by simultaneously finding multiple solutions of the parameter estimation problem. Estimation of the parameters of a finitely parameterized ODE based mathematical model from experimental data is required in many fields of science. This problem can be thought of as solving a system of nonlinear equations

$$\mathbf{f}(\boldsymbol{\theta}) = \mathbf{y}^*, \quad (1)$$

where  $\mathbf{f}$  is a map from  $\mathbb{R}^m$  to  $\mathbb{R}^n$ ,  $\boldsymbol{\theta}$  is the parameter vector, and  $\mathbf{y}^*$  is the experimental data. A standard approach for solving this type of system of nonlinear equations is a gradient based method such as the Newton method or the Levenberg-Marquard method. However, in the case of finding parameters from experimental data the problem may be more complicated than just solving (1) in the following ways, and standard nonlinear solvers may not be adequate:

- There is no guarantee that a solution to (1) exists, nor that it is unique.
- We often do not have a good initial guess for the parameter value  $\boldsymbol{\theta}$ .
- The experimental data contains a lot of error.

In order to overcome these challenges we have constructed a numerical algorithm called the Cluster Approximation method that approximately solves the system of nonlinear equations. This method differs from traditional nonlinear equation solvers in the following ways:

- It finds multiple possible solutions that approximately satisfy (1).
- It is more robust against local minima of the objective function compared to other gradient based algorithms since it constructs a linear approximation from multiple points.

- It is faster than population based stochastic methods as it is a gradient based algorithm.

Simply put, the Cluster Approximation method combines the desirable properties of a population based global optimization method (like semi-global convergence) with properties of gradient based methods (like convergence speed), as it moves a cluster of tentative solution points using gradient like information. We demonstrate these points through solving three different types of inverse problems in mathematical biology: underdetermined inverse problems (number of observations smaller than the number of parameters, i.e.,  $m > n$ ), overdetermined inverse problem (number of observations greater than the number of parameters, i.e.,  $m < n$ ), and parameter identifiability analysis problems (approximating an inverse image of a set).