Cluster Newton Method

An Algorithm for Solving Underdetermined Inverse Problem
Application to Parameter Identification for a Pharmacokinetics Model

Since the information we can obtain clinically from a live patient is often much less than the complexity of the internal activity in the patient's body, an underdetermined inverse problem appears in the model parameter identification problem for a mathematical model of a whole body drug kinetics.

We wish to sample multiple solutions of the underdetermined inverse problem to present the variety of possible solutions.

We propose a computationally efficient algorithm for simultaneously finding multiple solutions of an underdetermined inverse problem.

Example 1 : Level curve tracing (visual explanation of the algorithm)

Inverse Problem

Find a set of 100 points near $\mathcal{X}^0$, s.t.

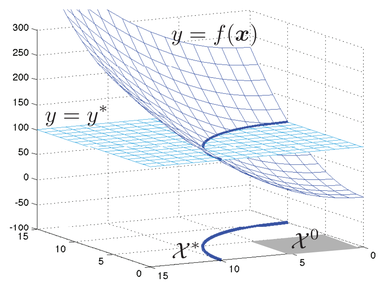
$$f(\boldsymbol{x}) = y^*$$

where

$$f(\boldsymbol{x}) = (x_1^2 + x_2^2) + \sin(10000x_1)\sin(10000x_2)/100$$

$$y^* = 100$$

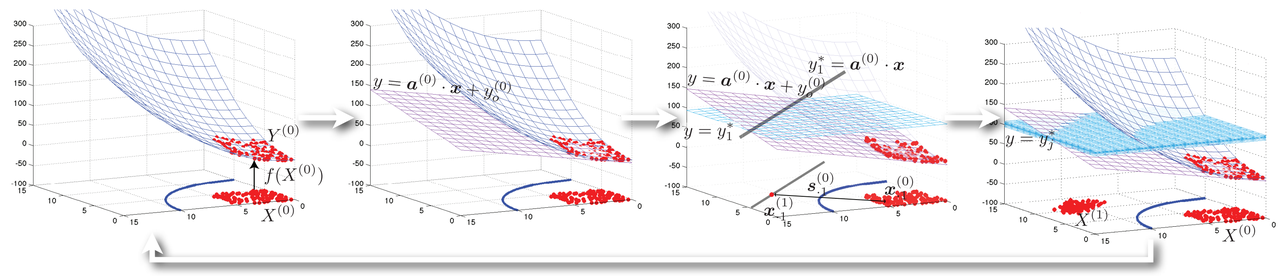
$$\mathcal{X}^0 = \{\boldsymbol{x} \in \mathbb{R}^2 : \max_{i=1,2}\left|\frac{x_i - 2.5}{2.5}\right| < 1\}$$



$\mathcal{X}^*$: solution manifold (approximately a circle of radius 10 centred at the origin)

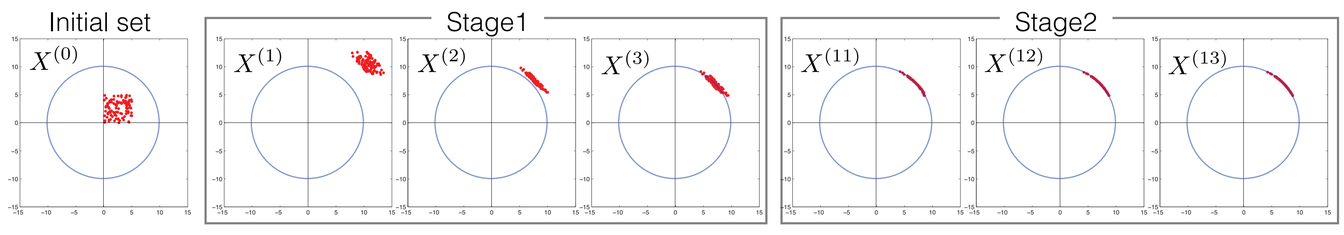
Algorithm : Cluster Newton method

- Stage 1 (Regularized Newton's method applied to a cluster of points)
  - Linear approximation with least squares fitting of a hyperplane (this step acts as a regularization against small 'roughness' in Example 1 or the error in the function evaluation in Example 2)
  - Moore-Penrose inverse using the linear approximation



- Stage 2 (Broyden's method, i.e. multi-dimensional secant method)
  - Use the linear approximation in Stage 1 as initial Jacobian (start with reasonable Jacobian approximation)
  - Use the points found by the Stage 1 as initial points (start with the initial points already close to the solution)

Result : Cluster Newton method



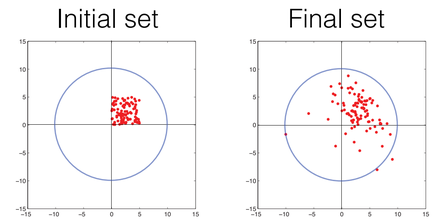
Algorithm : LM method

1: Randomly create 100 points in $\mathcal{X}^0$.

2: Use each point created in line1 as an initial point and use Matlab Optimization Toolbox (ver. 2010b) *fsolve* function (with the algorithm option set to Levenberg-Marquardt method).

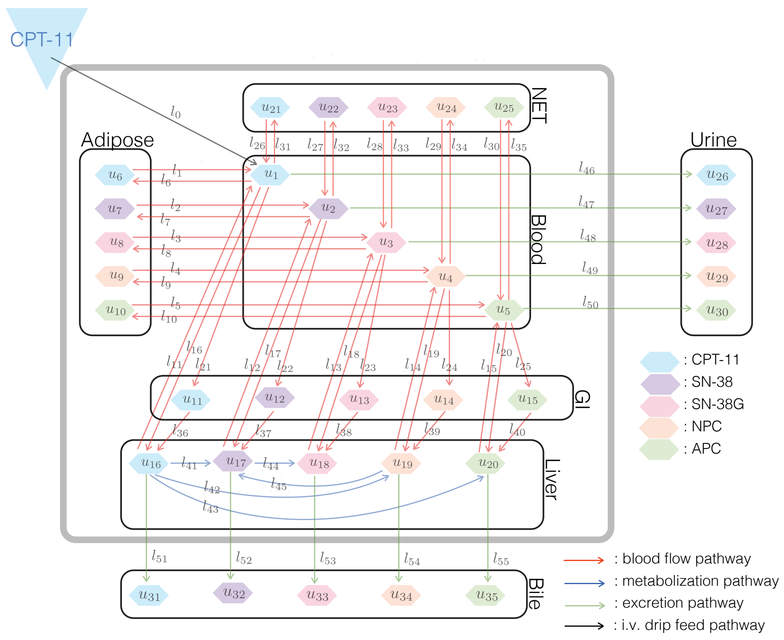
Result : LM method

For all of the initial points, the algorithm terminated with an error "Algorithm appears to be converging to a point that is not a root."



Example 2 : Parameter identification for a pharmacokinetics model (ODE coefficient identification)

Forward Problem
Pharmacokinetics model (Arikuma et al.)



ODE model for concentration of CPT-11 and its metabolites :

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{u} = \boldsymbol{h}(\boldsymbol{u}, t; \boldsymbol{x})$$

e.g., concentration of SN-38G in Liver:

$$\frac{\mathrm{d}}{\mathrm{d}t}u_{18} = \left(x_{53}\cdot u_3(t) + \frac{x_{52}}{x_8}\cdot u_{13}(t) + \frac{x_{45}\cdot x_{50}\cdot x_{57}}{\frac{x_{40}\cdot x_{12}}{x_{22}\cdot u_{17}(t)}+1}\frac{x_{52}+x_{53}}{x_{13}}\cdot u_{18}(t) - \frac{x_{33}\cdot x_{23}}{x_{13}}\cdot u_{18}(t)\right)/x_{57}\,.$$

$u_{1,\ldots,5}(\boldsymbol{x};t)$: concentration in blood (invasively measurable)

$u_{6,\ldots,25}(\boldsymbol{x};t)$: concentration in tissues (not measurable)

$u_{26,\ldots,35}(\boldsymbol{x};t)$: excretion amount in urine and bile (measurable)

$\boldsymbol{x}$: model parameters, (e.g. blood flow rate, amount/ reaction rate of enzyme, tissue volume)

t : time

T. Arikuma, S. Yoshikawa, R. Azuma, K. Watanabe, K. Matsumura, and A. Konagaya, "Drug interaction prediction using ontology-driven hypothetical assertion framework for pathway generation followed by numerical simulation", *BMC Bioinformatics*, 9(Suppl 6); S11, May 2008

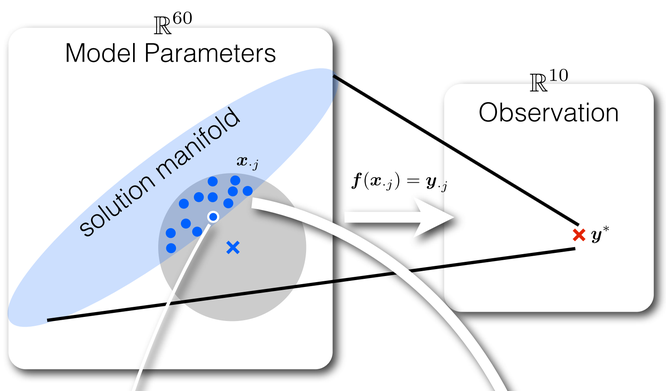
Inverse Problem
Model parameter identification

Estimate model parameters from non-invasive clinical observation, i.e., find $\boldsymbol{x}$ such that

$$\boldsymbol{f}(\boldsymbol{x}) = \boldsymbol{y}^*$$

where

$$f_i(\boldsymbol{x}) = u_{i+25}(\boldsymbol{x}; T) \qquad i = 1, 2, \ldots, 10$$

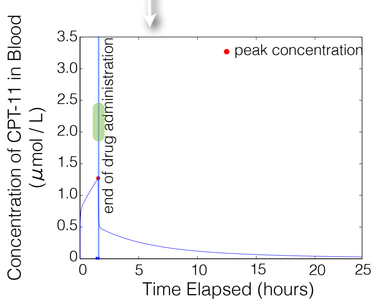


● : set of model parameters that reproduces the observation

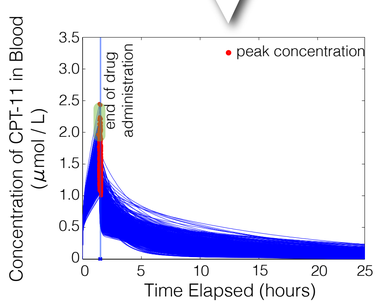
× : clinically observed data $\boldsymbol{y}^*$(Slatter et al.)

× : typical set of model parameters based on a-priori information (e.g., in vitro study of the metabolic reaction, clinically measured tissue volume)

Drug concentration prediction using a single set of parameters found by the Levenberg-Marquardt method with a typical value as the initial iterate.



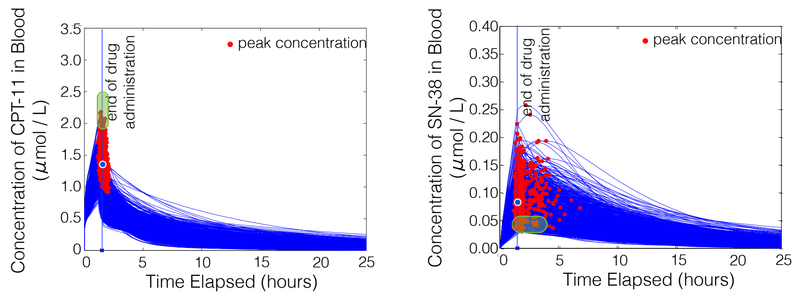
Drug concentration prediction using multiple sets of parameters found by the Levenberg-Marquardt method with multiple initial iterates.



J. G. Slatter, L. J. Schaaf, J. P. Sams, K. L. Feenstra, M. G. Johnson, P. A. Bombardt, K. S. Cathcart, M. T. Verburg, L. K. Pearson, L. D. Compton, L. L. Miller, D. S. Baker, C. V. Pesheck, and R. S. Lord III, "Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following i.v. infusion of [14c] CPT-11 in cancer patients", *Drug Metabolism and Disposition*, Vol. 28, No. 4, pp. 423:433, April 2000

Result

Drug and metabolite concentration prediction using multiple sets of parameters found by the Cluster Newton method.



● : peak concentration modeled using a single set of parameters found by the Levenberg Marquardt method with a typical value as the initial iterate.

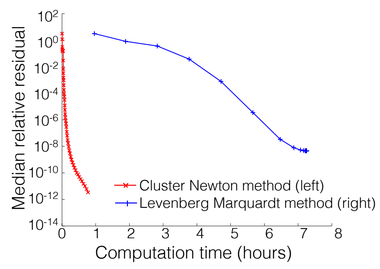
By sampling multiple sets of parameters, we have obtained realistic predictions of the concentrations of the drug and its metabolites.

<u>Levenberg-Marquardt method</u>

- Obtained multiple solutions by applying the method with multiple different initial iterates.
- Requires 469,439 function evaluations to find 1,000 solutions.

<u>Cluster Newton method</u>

- No local convergence even with the rough function evaluation at the earlier iterations.
- Requires 30,000 function evaluations to find 1,000 solutions.



Conclusion

We have introduced a new idea of sampling multiple solutions from the solution manifold of an underdetermined inverse problem.

We have proposed a new computationally efficient algorithm (Cluster Newton method) to simultaneously find multiple solutions of an underdetermine inverse problem (up to 100 times faster than multiple applications of the Levenberg-Marquardt method in Example 2).

Through numerical experiments, we have shown that this algorithm is fast accurate and robust solution method.

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