

Sampling Families of Solutions using the Cluster Newton Method for an Underdetermined Inverse Problem: Parameter Identification for Pharmacokinetics

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Question

If we are given the initial dose of the cancer fighting drug CPT-11 and the excretion profile of several cancer patients, can we find pharmacologically feasible parameters that describe the body's pharmacokinetics?

Contribution

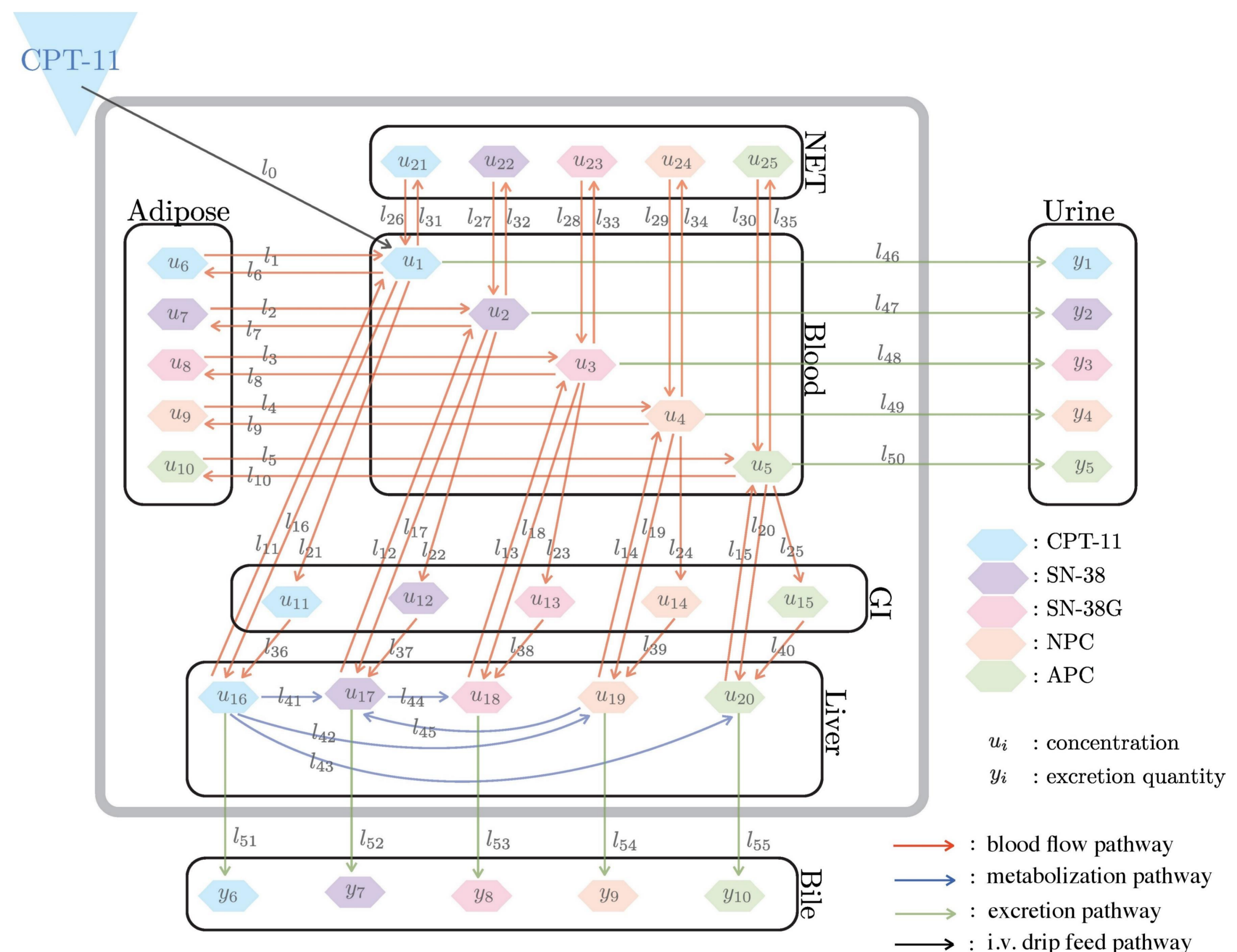
We created an algorithm based on the two parameters of the Beta distribution that enables the Cluster Newton Method to find multiple sets of pharmacologically feasible parameters .

Problem setting

In the field of pharmacokinetics, underdetermined inverse problems occur frequently. This is not surprising considering that the data that can be collected does not often explain the complex mechanics of the human body.

Through mathematical models, such as the PBPK model, we are able to simulate these complex behaviors and gain valuable insight on the body's pharmacokinetics.

The PBPK model



Underdetermined problems by nature have infinitely many solutions.

In the case of pharmacokinetics, we need extra constraints to restrain the variety of solutions.

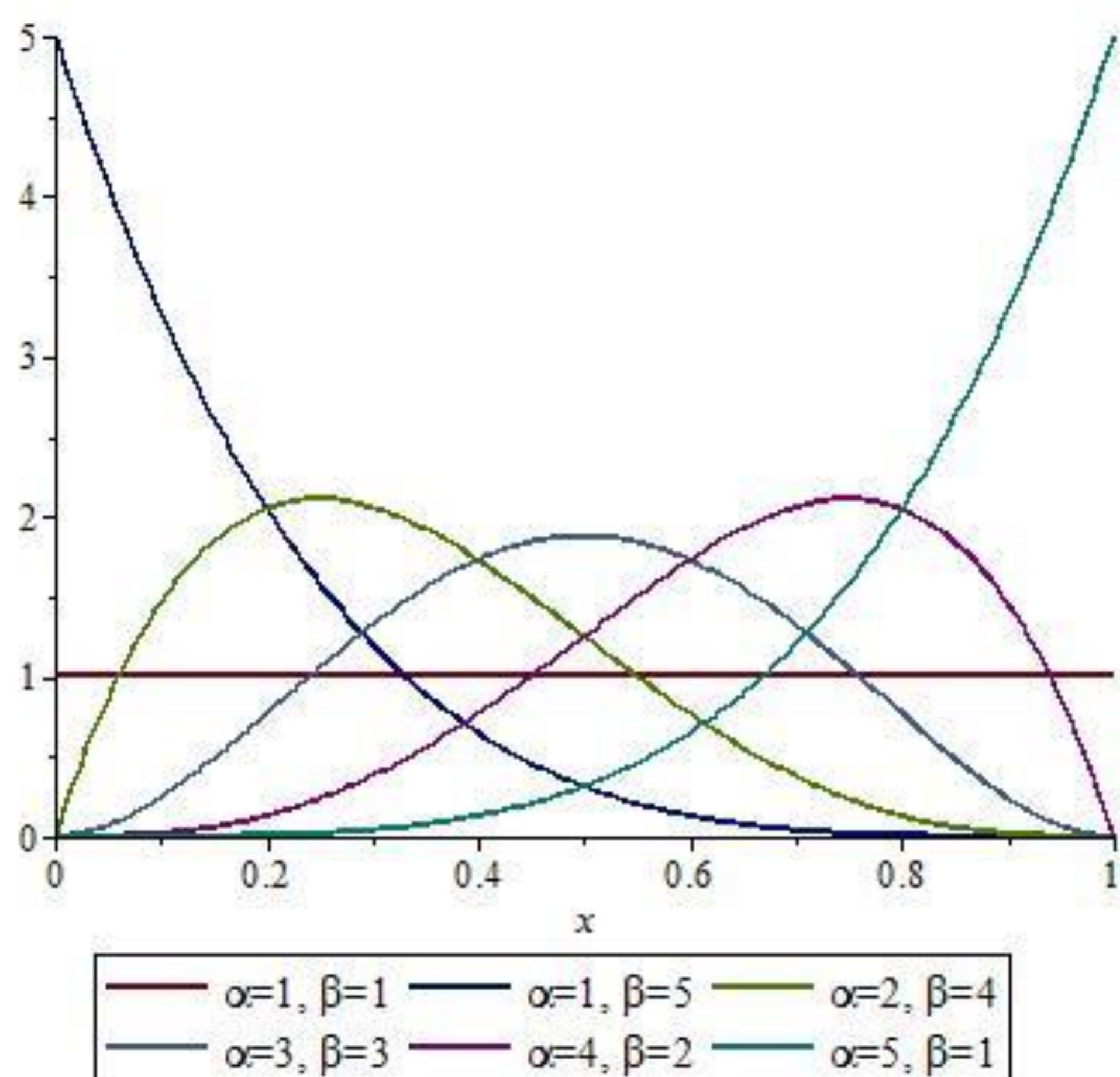
Find \mathbf{x} such that :

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

where \mathbf{y}^* is a given constant vector in \mathbb{R}^n , \mathbf{f} is a vector valued function from $\mathcal{X} \subset \mathbb{R}^m$ to \mathbb{R}^n with $m > n$

The Beta Algorithm

The Beta Distribution



$$\text{Mode}(\text{Beta}(\alpha, \beta)) = \frac{\alpha - 1}{\alpha + \beta - 2}$$

The Beta Algorithm

1 - Set up your initial conditions.

$(x_1^L, x_1^U) \leftarrow$ Implement CN method with uniform distribution in the range (x^L, x^U)

2 - For $m = 2, \dots, M$

Find the best fit solution with respect to experimental data.

$$x_{m-1}^* \leftarrow \min_{x \in \mathcal{X}_{m-1}} \left(\sum_{i=1}^p \sum_{j=1}^q \left| \frac{h_j(\mathbf{x}, \mathbf{u}(t_i, \mathbf{x})) - \hat{h}_{i,j}}{\epsilon_{i,j}} \right|^2 \right)^{1/2}$$

$(x_m^L, x_m^U) \leftarrow$ Implement CN method with $\text{Beta}(\alpha_i, D - \alpha_i)$

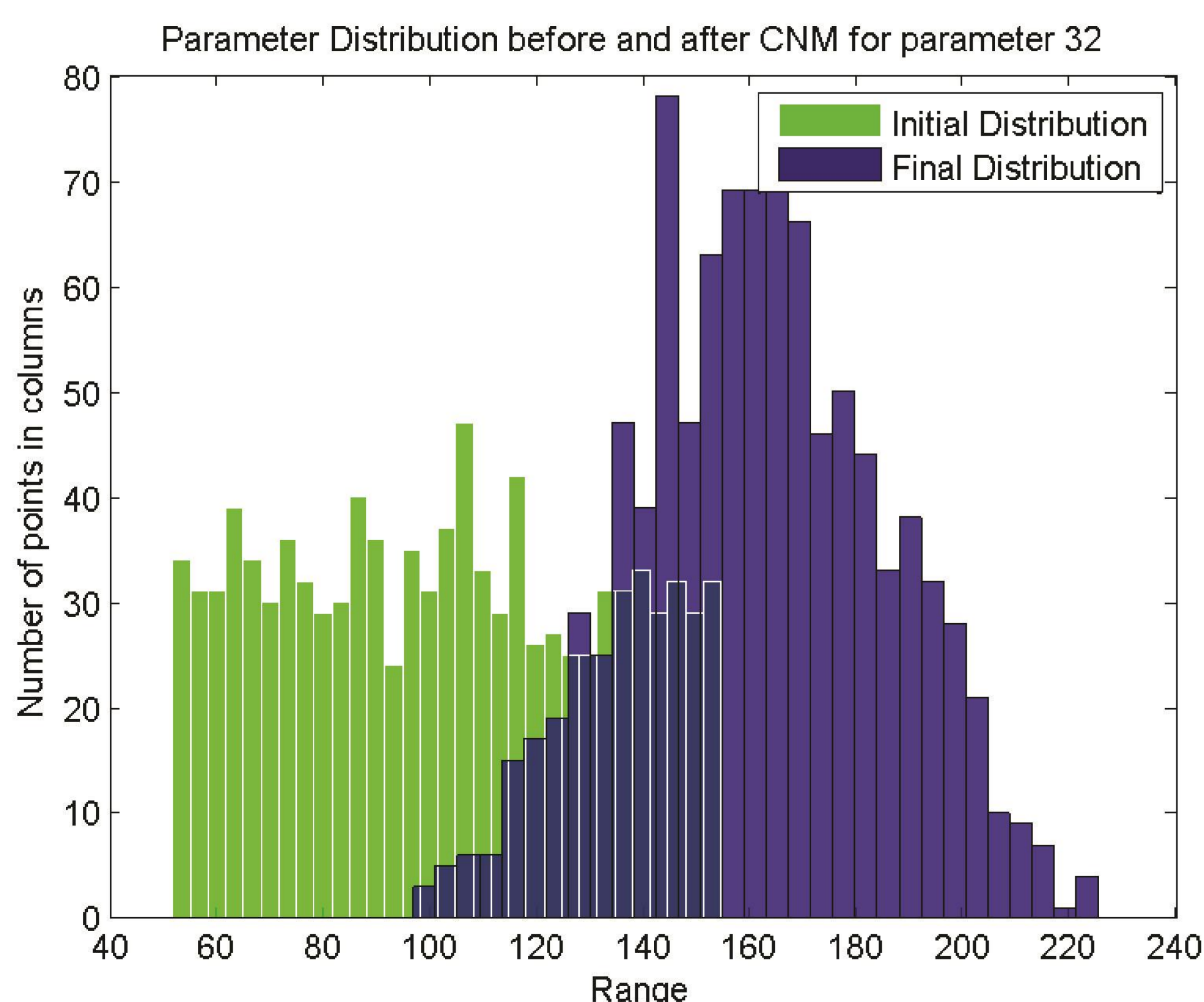
distribution in the range (x_{m-1}^L, x_{m-1}^U)

End for

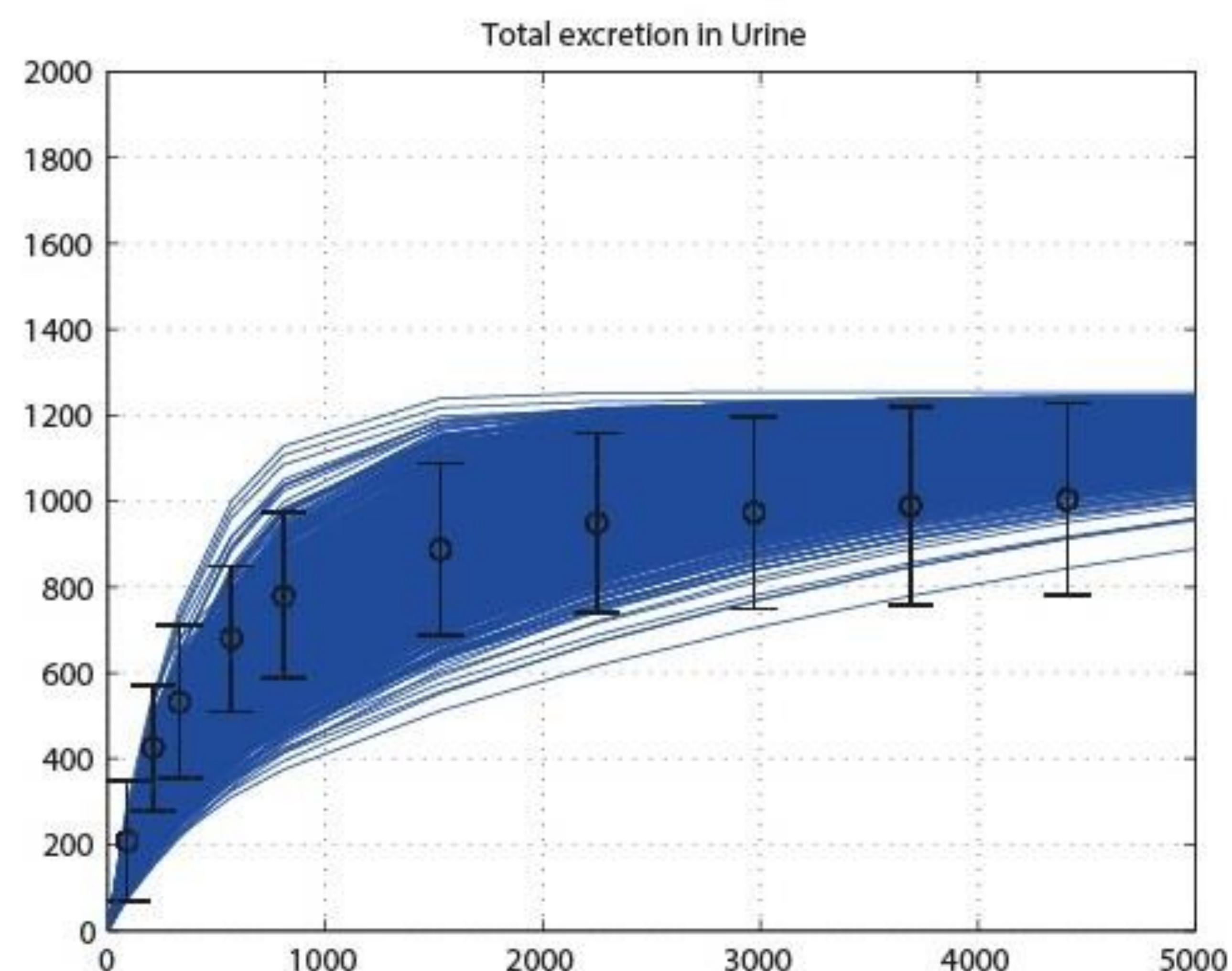
The Beta Algorithm can be summarized like so:

1. Find many uniformly distributed solutions using the Cluster Newton Method.
2. Find the solution that best fits the experimental data.
3. Use the Beta distribution to distribute new points around the best fit solution.
4. Using the Cluster Newton Method again, find many solutions around the best fit solution.

Our Results



The figure on the left displays the change in range of parameter 32 after using the Cluster Newton Method



This figure displays the total excretion of drug compounds in Urine. The blue lines are the solutions we found using the Beta algorithm.