

Numerical Optimization of Complex Instrumentation

A novel approach has been created for the selection of optimal instrument parameters that yield a mass spectrum which best replicates the molecular mass distribution of a synthetic polymer. The application of implicit filtering algorithms was shown to be a viable method to find the best instrument settings, while simultaneously minimizing the total number of experiments that need to be performed. This includes considerations of when to halt the iterative optimization process at a point when statistically significant gains can no longer be expected. This work represents part of an effort to develop an absolute molecular mass distribution polymer Standard Reference Material[®] by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry.

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Typical analytical instrumentation optimization is performed by the analyst by simply applying the “factory settings” or by “optimizing by eye.” This is because an exhaustive search of the parameter space for modern instrumentation with many adjustable parameters is prohibitively time consuming. However, a variety of little-known mathematical methods exist that enable the experimentalist to optimize instrument settings without performing an exhaustive search. Broadly classified, these methods are all forms of numerical optimization. When the topology of the search space is very complex, for example, when it has great sensitivity to one or more parameters (as mass spectrometers often do), the methods used are part of the field of non-linear programming. They are called non-linear because some (or all) of the instrument parameters do not have a linear relationship between parameter value and measurement response. A simple example is laser intensity in MALDI-TOF mass spectrometry and its effect on signal-to-noise ratio where a relatively sharp threshold is observed experimentally. When the measurement outcomes (which in the present case are mass spectra) contain random noise, the mathematical methods are termed stochastic numerical optimization. Stochastic methods are important in mass spectrometry because all mass spectra have noise, this noise varies as the instrument parameters are adjusted, and the noise will often change across the spectrum. Measurement noise presents a significant challenge to any optimization method especially for cases where signal to noise is not the measurand to be optimized. Nevertheless, numerical optimization methods offer experimentalists a way to tune the instrument parameters to achieve the desired goal without having to

search all possible parameter combinations. To measure the absolute molecular mass distribution of a synthetic polymer, it would be ideal to locate a region in parameter space where the instrument response function was uniform across the entire mass range. Finding the instrument response function is necessary to calibrate the intensity axis of the mass spectrum; that is, to go from mass spectrum to molecular mass distribution. If the instrument response function is uniform, then the relative peak areas in the mass spectrum correspond directly to the relative abundances of individual n-mers in the sample. A uniform instrument response function would be a line of zero slope; that is, it would have a derivative of zero. If not uniform, the instrument response function could slowly vary across the mass range, preferably linearly with mass. The optimal conditions are those that give the simplest (or flattest) instrument response function; that is, the one with the smallest derivative.

To measure the instrument response function, a gravimetric mixture was made of three low polydispersity polystyrenes that were very close in average molecular mass. The optimal instrument settings were those that provided the closest match between the total integrated peak intensity of each of the three polymers with the known gravimetric ratios. Note that there is no guarantee (or even assumption) that the optimal instrument settings that give the flattest instrument response function will also yield optimal signal to noise ratios. In fact there is no reason to believe that a search for the instrument settings that optimize the response function will not lead into a region where the mass spectra become so noisy as to make peak integration impossible. Thus, to find the optimal instrument settings, we used stochastic gradient approximation methods. These methods have proven to be extremely robust in cases where the measured data are very noisy.

Optimization is performed by defining an objective function $J(x)$ where x is a vector consisting of the instrument parameters. In our case, the objective function was the sum of the squared differences between the amount of each polymer in a mixture created gravimetrically, and the amount of each polymer in the mixture found by mass spectrometry. When this function is zero, the gravimetric concentrations match the concentrations found by mass spectrometry, and the instrument is optimized. The function $J(x)$ is a noisy function with respect to the parameter vector x , due to the inherent statistical noise in the mass spectra. This complicates the task of numerically locating the minimum of $J(x)$. The fact that each evaluation of $J(x)$ requires an experiment, and subsequent interpretation of experimental

results, means that there is a high cost for each function evaluation. This further complicates any numerical procedure that seeks to minimize $J(x)$. Finally, there are values of the vector x (for example, out of range instrument parameter settings), for which $J(x)$ cannot be evaluated. One method for minimizing noisy functions that seeks to approximate the gradient of the objective function is called implicit filtering. Broadly speaking, this method uses a very coarse grained step-length to build a finite difference approximation to the gradient of $J(x)$. This gradient is then used to generate steep-descent directions for a minimization process. As iterates draw closer to the solution, and the objective function decreases, the finite difference step-length is decreased until it approaches a number small enough to suggest convergence of the algorithm to the minimum value.

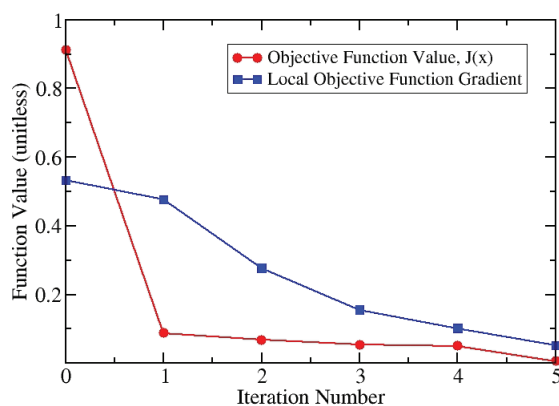


Figure 1: The objective function $J(x)$ and its local gradient value as a function of iteration step.

In Fig. 1, there is an initial steep drop in the objective function followed by gradual movement to the optimal parameter settings. The gradient of the objective function also decreases steadily as the optimum point is approached. These monotonic responses indicate that the optimization routine is stable. At the optimum value, the objective function is so small that it cannot be reduced further due to the inherent noise in the measurement. Likewise, the step size indicated for each parameter at this point is so small as to be below the precision of the instrument's settings.

In Fig. 2, the values oscillate about their final values as the optimization proceeds. The laser intensity undergoes the greatest excursions: decreasing in the first two iterations, returning to its initial value in the third iteration, and then increasing in the fourth iteration before settling into its final value. The four other parameters make an excursion in the direction of their final values in the first iteration, return to their initial value in the second iteration, and find the equilibrium values by the third iteration. This zigzag pattern is characteristic of the non-linearity of the system. This non-linearity arises from the fact that the instrument parameters are

coupled; that is, varying one requires all others to vary in response if $J(x)$ is to move closer to its optimal value. Thus, the vector x_{i+1} has a tendency to be normal to the vector x_i (in its five-dimensional space). The laser intensity varies the most, and would seem to be the dominant variable. It seeks its stable value before the other parameters can settle down to find their optimal values.

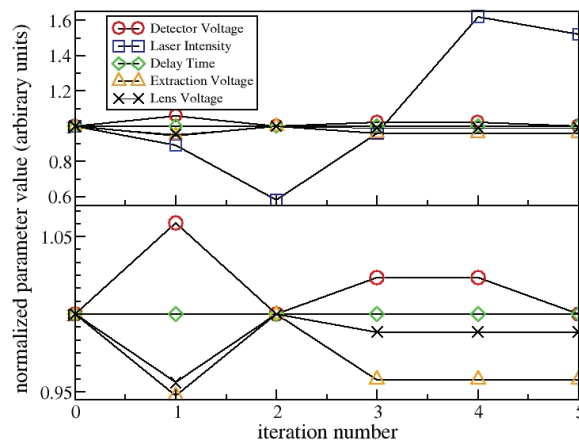


Figure 2: Individual instrument parameter values as a function of iteration number.

A specialized noise-adapted filtering method has been applied to the problem of finding the optimal instrument parameters for a MALDI-TOF mass spectrometer. Finding the optimal instrument parameters was a critical step in creating an absolute molecular mass distribution polymer Standard Reference Material[®]. The task of tuning the instrument's five main parameters could not be approached by exhaustive search methods, given the amount of effort needed to take and to reduce the data in a statistically meaningful way at each set of instrument parameters. Additionally, this method produces an estimate of the sensitivity of each optimal parameter not available to traditional exhaustive search methods. Each of the subtasks in the process could be automated to create an integrated closed-loop optimization scheme.

For More Information on This Topic

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