Using Machine Learning to Maintain Instrument Reliability

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SUMMARY

Good peak shape versus bad peak shape. Predicting optimal values. Lots of data. This describes challenges in LC-MS, but it also describes an opportunity for using established machine learning and optimization strategies. Classifiers can be trained and used for identifying spectral peaks that 'look bad' to the human eye. Optimal lens voltages can be obtained without searching all possible values using optimization algorithms.

Most QTOF instruments have many lenses used to guide and focus ions from the quadrupole filters and collision cell into the TOF region. These lenses often have interdependencies, where the optimal value for one lens will impact the optimal value on another lens. Searching all possible values becomes impractical if there are more than a few such lenses. A version of a genetic algorithm was used to reduce this search space to something more reasonable. Voltages were treated as swappable genes. Fitness was measured as a score combining resolution and intensity of the signal. An initial population was created using random values, high fitness instances were kept and paired off to create a new generation. Within a small number of iterations, this strategy converges on an optimal set of voltages.

Recently, machine learning has found wide spread adoption in any field where classifying objects is important. One example where this can be used in mass spectrometry is when tuning an instrument. Occasionally, an instrument will meet typical performance characteristics such as peak width and intensity, but it will not meet expectations about peak shape quality. In other words, it just looks bad. A rules-based approach can sometimes succeed at identifying these poor quality peaks, but it requires adjustments and tolerances for every new instrument or peak. Classifiers such as random decision forests or support vector machines achieved a high level of success at classifying good versus poor quality spectral peaks.

MATERIALS AND METHODS

The TripleTOF® 6600 system. Infusing CsI / peptide calibration solution. Analyst® TF 1.7.1 software using research version of Instrument Optimization. Used for genetic algorithm development.

X500R QTOF system. Infusing calibration solution. SCIEX OS 1.4. The X500R has a simplified ion path with fewer dependent lenses. The genetic algorithm was not required for tuning this instrument.

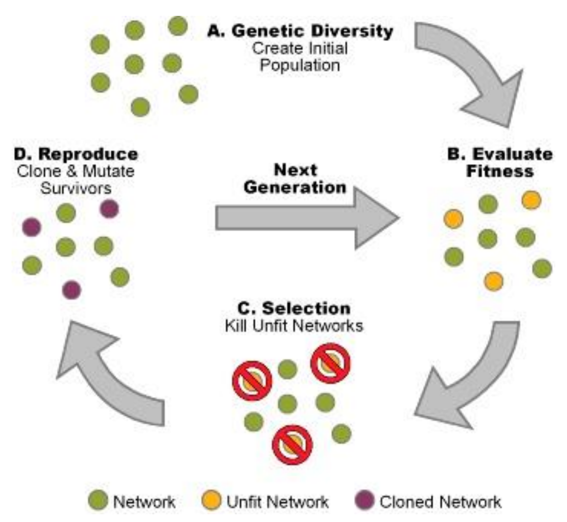
Prototype of QTRAP® 6500+ system. Infusing PPG tuning solution. Tuning Tools software research version. Data analysis in PeakView® and Weka 3: Data Mining software. Used for SVM peak shape classifying.

Triple TOF System

The TripleTOF 6600 system ion path. To transfer ions from the collision cell to the TOF detector requires a number of lenses. These lenses control how much energy the ions have, how the ions are steered left/right or up/down, how focused the ions are entering and exiting the pusher, how much voltage is required to reflect the ion, and more. Working together, they enable the instrument to achieve high resolution and sensitivity. When the instrument is close to optimal tuning, finding the optimum is a simple matter of ramping one lens voltage, choosing the best performing value, ramping the next lens voltage, and so on. With an untuned, newly manufactured instrument this simple procedure can occasionally fail to find a suitable optimum. The dependencies between some lenses can result in a local maximum being found, but not the global maximum.

If all possible combinations for the typical voltage range of these lenses was tried by brute force (1 second accumulation time) it would take roughly 2.3 million years to complete.
One class of algorithms useful in reducing the time it takes to find a global maximum is the genetic algorithm. This algorithm works similar to how genetic variation leads to organisms optimally fitting into their environment.
In general, an in initial population of various attributes (genes) is selected, the fitness of each unit is evaluated (Figure A). Some units are eliminated, while the remaining ones are used to create a new generation. Children are generally similar to a mixture of their parents (cross-over), with some randomness (mutations).
For mass spectrometer tuning, each lens is treated as a gene. The voltage applied to that lens is the value for that gene. A specific set of voltages for all lenses comprises an individual unit. Fitness is evaluated as a combined score of resolution and intensity for an infused standard (CsI / Peptide calibration solution). A new generation of units is created by randomly pairing units, but weighted by their fitness score. High fitness units will create more offspring than low fitness units. The value of the lenses for each new generation unit will be a random value between the value of its parents. In addition some random changes (mutations) in voltages are introduced. Mild mutation involve a small step in voltage in a random direction. Severe mutations involve a completely random voltage value for that lens. This new generation is evaluated and the process is repeated.
In practice, 10 generations of testing results in coalescence around an optimal tuning set (Figure B). Often, this value is still slightly less than the absolute best performance the instrument can achieve. However, it is close enough that a simple ramping procedure can now find the true optimum in short order (Figure C). The entire tuning procedure takes 10-15 minutes.

A



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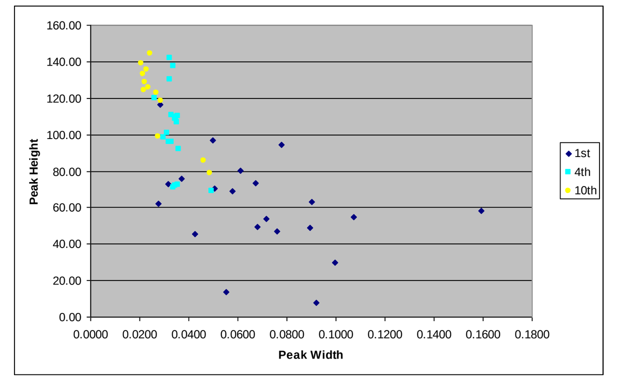
B



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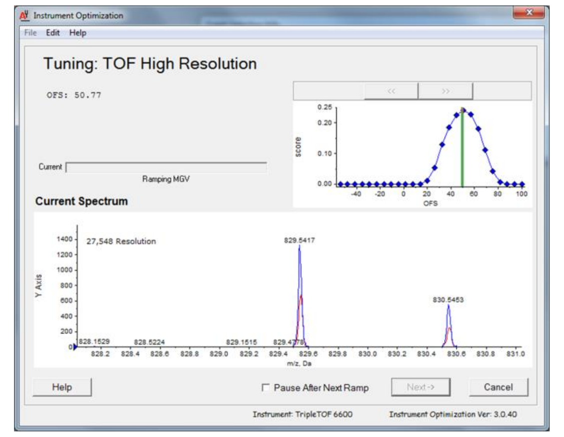
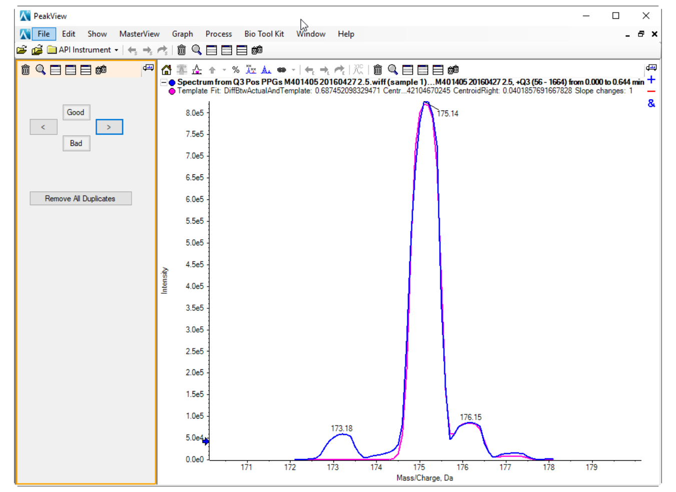
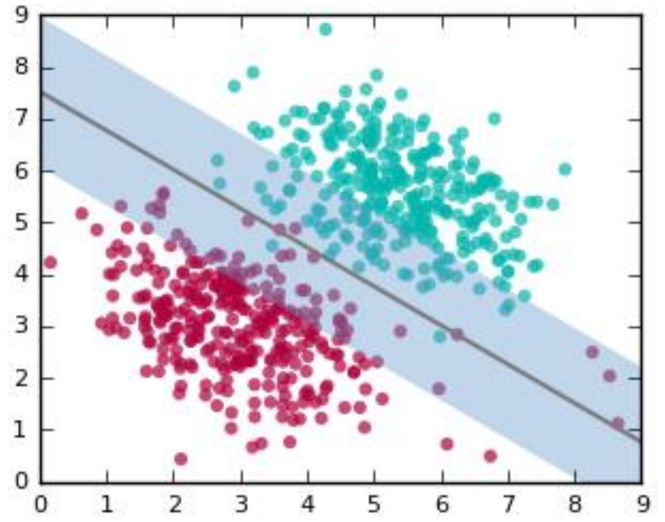


Triple Quadrupole / QTRAP System

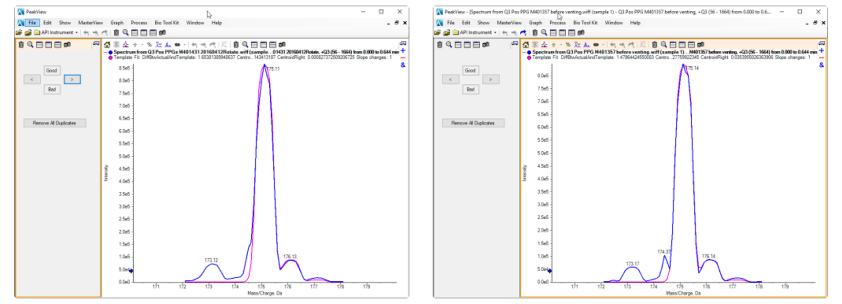


Another challenge in instrument tuning is achieving acceptable peak shape while surpassing intensity and peak width specifications. Peak shape is difficult to define with a single measurement that classifies 'good' from 'bad'. It falls into a class of categorizers best described as "I know it when I see it".

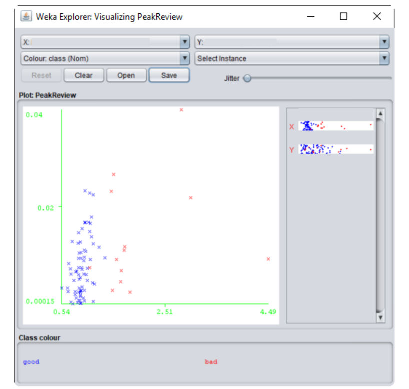
Several machine learning algorithms can be used for classification. A commonly used one is a support vector machine (SVM), which is easiest to understand with a picture. Consider a set of data that has been classified (good/bad), and a couple of measures of this data (perhaps width and peak asymmetry). You can draw a line, or a road (a line with thickness), that separates as many of these points as possible. AN SVM draws a line that tries to maximizes the thickness of this road.
If something can be classified based on a single measurement (width pass or fail), then it is easier to set a decision level on that single measure. However, when a decision is based on several different measures, it is easier to focus effort on generating examples of good and bad and letting an SVM perform the classification.



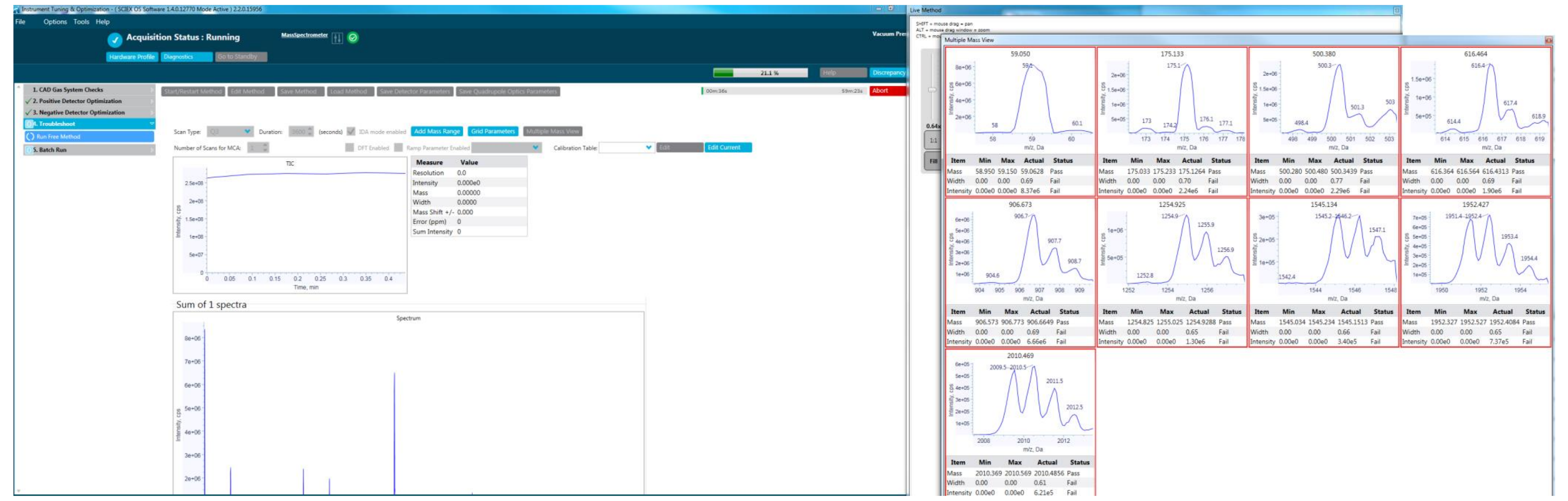
https://www.kdnuggets.com/2017/08/support-vector-machines-learning-svms-examples.html



Examples of peak shapes that meet most performance criteria (width and intensity) but have a small artifact. If not caught early in manufacturing / tuning, it can lead to significant loss of time to retune the instrument.



Weka 3: Data Mining Software was used for visualizing the measures and training an SVM (LIBSVM). The resulting model was then used in a manufacturing software tool for classifying peaks based on shape.



Typical view in manufacturing software for evaluating peaks. Peaks would have width and intensity specifications. Peak shape classification can now be added as a specification.

CONCLUSIONS

- **Genetic algorithm used to reduce TOF instrument tuning from a theoretical 2.3 million years to typically 10 minutes.**
- **Support vector machine used to classify 'good' from 'bad' peak shape during quadrupole tuning**

REFERENCES

1. Aurélien Géron. Hands-On Machine Learning with Scikit-Learn and TensorFlow. O'Reilly books 2017.

TRADEMARKS/LICENSING

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