

THE UNIVERSITY OF ALABAMA  
DEPARTMENT OF CHEMISTRY  
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APPLICATIONS OF THE HADAMARD  
TRANSFORM IN ANALYTICAL  
CHEMISTRY

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Literature Seminar  
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## INTRODUCTION

Modern analytical chemistry has long been dependent on the development of instruments and measurement techniques. In most cases, changes in a specific property of the studied matter, such as optical, electrical, magnetic, acoustic, etc., is utilized to acquire the needed data. In addition, new methodologies developed in mathematical, computer, biological sciences as well as other fields have helped provide in-depth and broad-range analyses<sup>1</sup>. In the past, the primary problem confronting analytical scientists was how to obtain data, because the process was mostly manual and time consuming, and provided low sensitivity. But with the development of modern instrumental techniques, sampling has become much faster and precise. In many regards, the research focus of analytical chemistry has gradually shifted more towards data processing, which has led to a new subdiscipline: chemometrics.

Chemometrics concerns with the application of statistical and mathematical methods, as well as those methods based on mathematical logic, to chemistry<sup>2</sup>. With chemometrics, new mathematical, logical as well as computer techniques are employed to analytical measurements and make the measurements no longer used only to acquire data from chemical experiments. There are techniques for collecting better data (e.g., design of experiments, optimization of experimental parameters, calibration, and signal processing) and extracting more information from these measured data (e.g., statistical analysis, modeling and pattern recognition).

Within these techniques, transform techniques offer three main advantages for chemists<sup>3</sup>. First, transform techniques provide a variety of simple procedures for handling digital data: smoothing or filtering to enhance signal-to-noise ratio (SNR); resolution enhancement; changing spectral line shapes (such as from Lorentzian to Gaussian); generation of integrals or derivatives; and clipping to reduce data storage requirements. Second, Fourier methods can be used to remove any known irregularities in the excitation waveform, so that the corrected response reflects only the properties of the sample, and not the effect of the measuring instrument. Third, coded or multiplex detection followed by Fourier or Hadamard decoding can offer a multiplex

advantage<sup>4</sup> (Fellgett advantage) of up to  $\sqrt{N}$  in SNR or  $1/N$  in time compared to a scanning instrument, where  $N$  is the number of data points in the frequency spectrum.

The Hadamard transform is an example of a generalized class of discrete Fourier transform (DFT) which performs an orthogonal, symmetric, involuntary linear operation on  $2^m$  numbers. The transform is named for the French mathematician Jacques Hadamard because it involves a special square matrix - Hadamard matrix.

In reality, the Hadamard transform is not a total new concept to analytical chemistry. The possibility of realizing the multiplex advantage with a grating spectrometer by means of optical coding based on Hadamard matrix was first pointed out by Ibbett *et al.*<sup>5</sup> and Decker *et al.*<sup>6</sup> in 1968. Shortly afterwards, Sloane *et al.*<sup>7</sup> and Pratt *et al.*<sup>8</sup> described the mathematical properties of Hadamard transform multiplexing codes. Since then the Hadamard transform has been widely used for more than 30 years in optical spectroscopy. Since optical and other spectra are widely employed in analytical chemistry, the Hadamard transform has thus been used in analytical chemistry for a long time<sup>9</sup>.

Recently there have been many new applications of the Hadamard transform, particularly in time-of-flight mass spectrometry (TOF-MS)<sup>10</sup>, capillary electrophoresis (CE)<sup>11</sup>, ion mobility spectrometry<sup>12</sup>, and fluorescence microscopy image processing<sup>13</sup>. Also Hadamard matrix can be used in experimental design<sup>14</sup>. This review will focus on the basic principle of Hadamard transform and its applications to TOF-MS and CE.

## PRINCIPLES

### 1. Multiplexing

The concept of multiplex was first suggested in 1935 by Yates<sup>15</sup>. The basic idea is weighing the objects in groups rather than one at a time can lead to the determination of the individual weights more accurately.

Here is a simplified example:

We use a single pan spring balance to weigh four objects, numbered as 1, 2, 3, and 4. We assume the balance has been well calibrated and every time it will give us the correct value (true value  $\Psi$ ) with a small random error ( $e$ ). The average of  $e$  is 0, but the average of  $e^2$  is not 0, which is the variance of  $e$  (mean squared error  $\sigma^2$ ). If we simply weigh the objects one by one, we can get 4 measurements  $\eta_1, \eta_2, \eta_3, \eta_4$  :

$$\eta_1 = \Psi_1 + e_1$$

$$\eta_2 = \Psi_2 + e_2$$

$$\eta_3 = \Psi_3 + e_3$$

$$\eta_4 = \Psi_4 + e_4$$

The mean squared error is  $\sigma^2$ .

On the other hand if we measure 3 objects per weighing, we can get another set of results:

$$\eta_1 = \Psi_1 + \Psi_2 + \Psi_3 + e_1$$

$$\eta_2 = \Psi_2 + \Psi_3 + \Psi_4 + e_2$$

$$\eta_3 = \Psi_1 + \Psi_3 + \Psi_4 + e_3$$

$$\eta_4 = \Psi_1 + \Psi_2 + \Psi_4 + e_4$$

Then we can calculate the weight of each object:

$$\hat{\Psi}_1 = \frac{1}{3}(\eta_1 + \eta_3 + \eta_4 - 2\eta_2)$$

$$\hat{\Psi}_2 = \frac{1}{3}(\eta_1 + \eta_2 + \eta_4 - 2\eta_3)$$

$$\hat{\Psi}_3 = \frac{1}{3}(\eta_1 + \eta_2 + \eta_3 - 2\eta_4)$$

$$\hat{\Psi}_4 = \frac{1}{3}(\eta_2 + \eta_3 + \eta_4 - 2\eta_1)$$

Subsequently we can get the estimate weight of each object:

$$\hat{\Psi}_1 = \Psi_1 + \frac{1}{3}(e_1 + e_3 + e_4 - 2e_2)$$

$$\hat{\Psi}_2 = \Psi_2 + \frac{1}{3}(e_1 + e_2 + e_4 - 2e_3)$$

$$\hat{\Psi}_3 = \Psi_3 + \frac{1}{3}(e_1 + e_2 + e_3 - 2e_4)$$

$$\hat{\Psi}_4 = \Psi_4 + \frac{1}{3}(e_2 + e_3 + e_4 - 2e_1)$$

The mean squared error for object 1 is:

$$\epsilon_1 = (\hat{\Psi}_1 - \Psi_1)^2 = \frac{5}{9}\sigma^2 = \epsilon_2 = \epsilon_3 = \epsilon_4$$

It is a considerable improvement because the variance in the measurement is reduced to  $\frac{5}{9}$  of original variance. With different weighing method, different optimized variance can be obtained.

The weighing problem can be easily changed into an analytical chemistry problem. For example, we do the following transformation:

Objects to be weighed	into	Wavelength range to be measured
Weight	into	Emission or absorption
Balance	into	Optical detector

then the weighing problem is changed into a spectrum measurement problem. If the measurement cost for multiple objects is about the same as the cost for a single object, it is advantageous to take advantage of multiplexing for this measurement.

## 2. Hadamard matrix

Returning back to the weighing problem, if a two-pan balance is used we can optimize the weigh design and get a better result.

$$\eta_1 = \Psi_1 + \Psi_2 + \Psi_3 + \Psi_4 + e_1$$

$$\eta_2 = \Psi_1 - \Psi_2 + \Psi_3 - \Psi_4 + e_2$$

$$\eta_3 = \Psi_1 + \Psi_2 - \Psi_3 - \Psi_4 + e_3$$

$$\eta_4 = \Psi_1 - \Psi_2 - \Psi_3 + \Psi_4 + e_4$$

The measurement with negative value means that object is placed on the right pan of the balance.

The estimate weight of each object is:

$$\hat{\Psi}_1 = \frac{1}{4}(\eta_1 + \eta_2 + \eta_3 + \eta_4) = \Psi_1 + \frac{1}{4}(e_1 + e_2 + e_3 + e_4)$$

$$\hat{\Psi}_2 = \frac{1}{4}(\eta_1 - \eta_2 + \eta_3 - \eta_4) = \Psi_2 + \frac{1}{4}(e_1 - e_2 + e_3 - e_4)$$

$$\hat{\Psi}_3 = \frac{1}{4}(\eta_1 + \eta_2 - \eta_3 - \eta_4) = \Psi_3 + \frac{1}{4}(e_1 + e_2 - e_3 - e_4)$$

$$\hat{\Psi}_4 = \frac{1}{4}(\eta_1 - \eta_2 - \eta_3 + \eta_4) = \Psi_4 + \frac{1}{4}(e_1 - e_2 - e_3 + e_4)$$

The mean squared error is

$$\epsilon_1 = (\hat{\Psi}_1 - \Psi_1)^2 = \frac{1}{16} \times 4\sigma^2 = \frac{1}{4}\sigma^2 = \epsilon_2 = \epsilon_3 = \epsilon_4$$

The result is much better than a single-pan balance result. When the corresponding weighing matrix is written down, we get a Hadamard matrix of order 4:

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \end{bmatrix}$$

A Hadamard matrix is a square matrix whose rows are mutually orthogonal and the elements in the matrix are either +1 or -1<sup>16</sup>. The simplest Hadamard matrix is [1]. In 1867 Sylvester provided a method to construct Hadamard matrix of order 2n: If H is a Hadamard matrix of order n, then  $\begin{bmatrix} H & H \\ H & -H \end{bmatrix}$  is a Hadamard matrix of order 2n<sup>17</sup>.

These Hadamard matrices can be used in the measurements, but sometimes a negative value is not possible or not economical for the measurement. For example, the optical spectrum measurement we can use two detectors of the same type to simulate the two pans of the balance, but if we can use one detector it will be more economical and stable. Constructing a weighing matrix only with elements 0 and 1 is more suitable for this kind measurement. Sylvester matrix is one of this kind matrix which is derived from Hadamard matrix. Deleting the first column and row and changing 1s to 0s and -1s to 1, a Hadamard matrix of order n becomes a Sylvester matrix of order n-1.

$$S_1 = [1], \quad S_3 = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \\ 1 & 1 & 0 \end{bmatrix}$$

$$S_7 = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 1 \\ 1 & 0 & 1 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 & 1 \end{bmatrix}$$

When using Sylvester matrix in measurement, 1/0 can be easily converted into on/off or yes/no states. Sylvester matrix is also called as simplex matrix or s-matrix.

### 3. Hadamard transform

In traditional spectral measurement, the intensity of each wavelength is measured one at a time. Figure 1 shows the scheme of the traditional spectrometer. A monochromator (grating or prism) with a single slit mask is used to obtain single wavelength light at a time. A full spectrum with N different wavelength points can be obtained by changing N times the monochromator output wavelength.

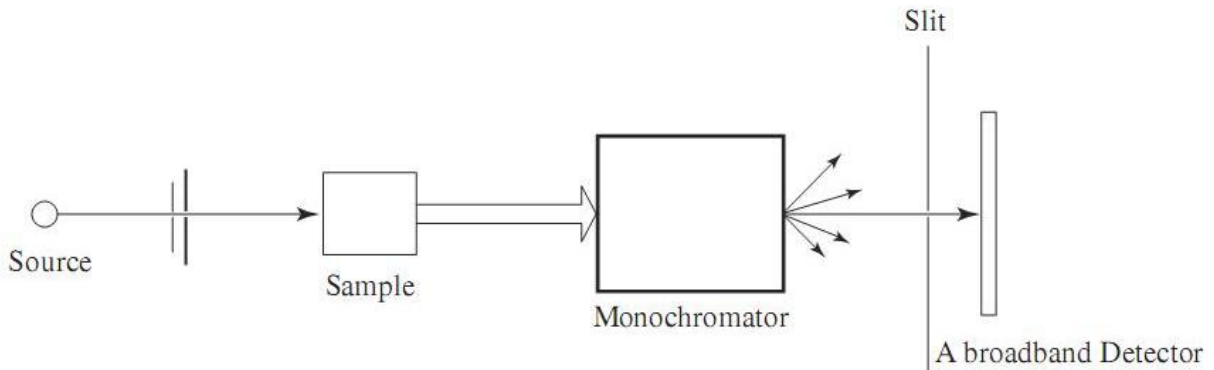


Figure 1. Schematic diagram of a conventional single-slit scanning spectrometer.

To take advantage of multiplexing, a Sylvester matrix encoded mask is applied. Slots on the mask stand for 0s and 1s in the matrix. For example, a  $S_7$  matrix coded mask can be read as string 1010101011001111001100001111101101001111001101001.



Figure 2. 255 slots encoded mask for Hadamard transform spectrometer<sup>18</sup>.

A schematic diagram of Hadamard transform spectrometer is shown as Figure 3. The monochromator helps generate light of different wavelength. The Hadamard transform encoded mask allows several light beams of different wavelength to reach the detector simultaneously. By scanning the different part of the mask, we get the intensity matrix  $m$ . If the single wavelength intensity matrix is  $x$ , then  $m = Hx$ , here  $H$  is the Hadamard matrix or Sylvester matrix which encodes the mask,

$$x = H^{-1}m$$

Because the absolute value of every element in the Hadamard matrix is 1, for a Hadamard matrix of order  $n$ ,  $H^{-1} = \frac{1}{n}H$ , then we can get the final spectrum by

$$x = \frac{1}{n}Hm$$

This process is called the Hadamard transform, and the spectrum is called Hadamard transform spectrum (HTS). The HTS can enhance the SNR by  $(N + 1)/2\sqrt{N}$  times<sup>19</sup>. When the  $N$  is large enough, the increase signal-to-noise ratio is  $\sqrt{N}/2$ .

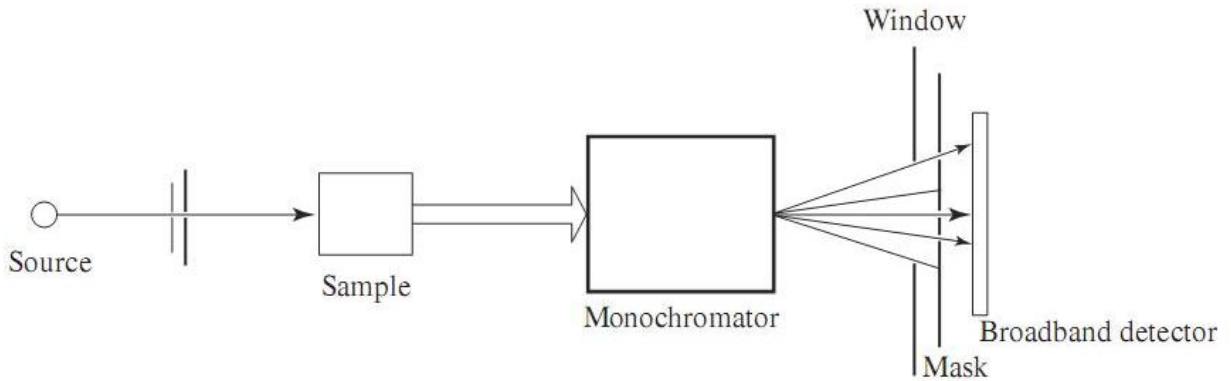


Figure 3. Schematic diagram of the Hadamard multichannel spectrometer.

## APPLICATIONS

The Hadamard transform is not only applied in optical spectroscopy, such as infrared spectroscopy (IR)<sup>20</sup>, but also other analytical measurements to increase SNR or instrument sampling efficiency.

### 1. Hadamard transform time-of-flight mass spectrometry (HT-TOFMS)

Mass spectrometry (MS) is an analytical technique used to measure the mass-to-charge ratio of ions by a mass spectrometer which converts neutral molecules into ions and separates the ions in known electric and/or magnetic fields. MS has several applications, including<sup>21</sup>:

- identifying unknown compounds by the mass of the compound molecules or their fragments
- determining the isotopic composition of elements in a compound
- determining the structure of a compound by observing its fragmentation
- quantifying the amount of a compound in a sample using carefully designed methods (MS is not inherently quantitative)
- studying the fundamentals of gas phase ion chemistry (the chemistry of ions in vacuum)
- determining other physical, chemical, or biological properties of compounds with a variety of other approaches

There are a large number of mass spectrometric methods used in mass analyzer: magnetic sector, time-of-flight (TOF), quadrupole, ion trap, and Fourier transform ion cyclotron resonance (FT-ICR). Among these analyzers, TOF analyzer is considered as the simplest one which was introduced in 1955<sup>22</sup>. TOF is favorable because of its high ion transmission, essentially unlimited mass range, high repetition rate, good resolution, and modest cost<sup>23</sup>. With electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI) ion source, TOF is also used to analyze mixtures of peptides.

The schematic diagram of TOF is shown in Figure 4. The ions are introduced by ion source as a pulse and receive the same initial kinetic energy.

$$E_k = E_p = zeV$$

As they then pass along the field free drift zone, they are separated by their masses, lighter ions travel faster. The time of flight of the ion varies with the square root of its mass-to-charge ratio.

$$E_k = \frac{1}{2}mv^2 = zeV$$
$$v = \frac{d}{t}$$

$$zeV = \frac{1}{2}m\left(\frac{d}{t}\right)^2$$

$$t = \frac{d}{\sqrt{2eV}}\sqrt{\frac{m}{z}}$$

This enables the instrument to record all ions as they arrive at the detector and so accounts for the techniques high sensitivity.

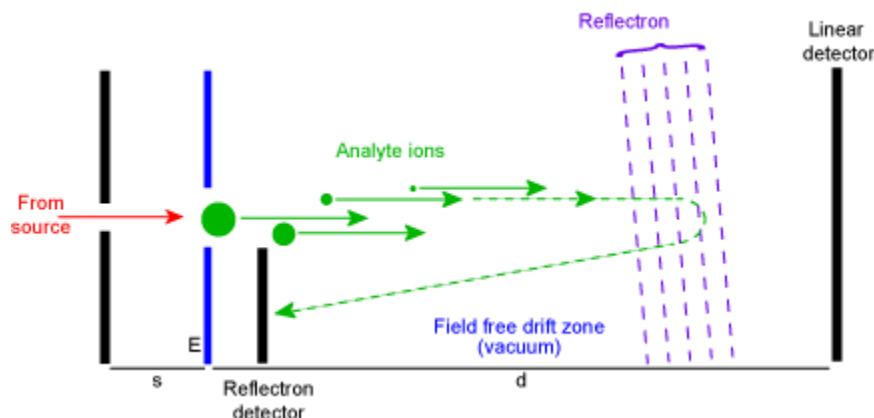


Figure 4. Schematic diagram of TOFMS operating in Reflectron Mode.

The conventional TOFMS introduces ions packets as a pulse, so the interface between a continuous ion source and the TOFMS needs to deal with two compromising requirements. First, increasing the resolution of the masses requires bringing the ions with as little spatial and kinetic energy spread as possible into the spectrometer. Second, achieving a high duty cycle need using as much of the ions supplied by the continuous source as possible without compromising on the first requirement. Today, the preferred solution to these problems is orthogonal acceleration (OA)<sup>24</sup>. The ion beam should enter the spectrometer at a right angle with respect to the flight axis of the ions in the spectrometer in order to meet the first requirement. The second requirement is met by extending the width of the extraction region so that a larger fraction of the ion beam can be sampled. Typical duty cycles are 20%-30% with a resolution of 10,000 for OA solution.

Zare *et al.* described and demonstrated a new mode of operation of TOFMS<sup>25</sup>. It modulates the continuous ion source and detector with a pseudorandom sequence and is named

as Hadamard transform time-of-flight mass spectrometry (HT-TOFMS). A higher duty cycle can lead a high signal-to-noise ratio due to more species introduced and more signals being detected.

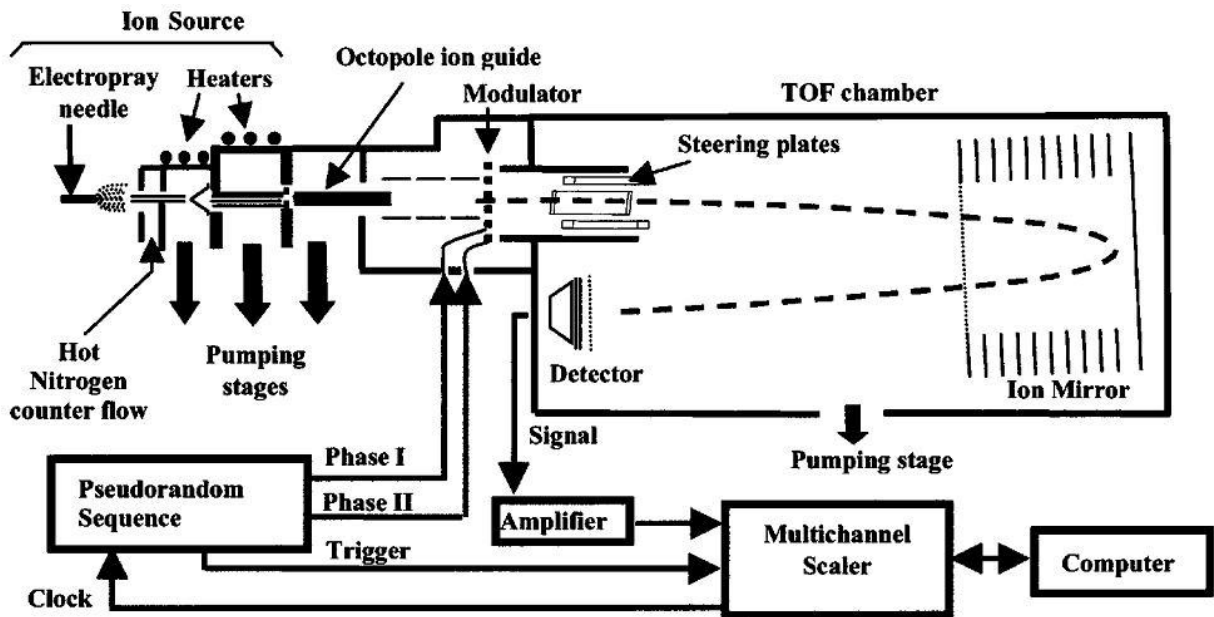


Figure 5. Schematic diagram of HT-TOFMS<sup>26</sup>.

The schematic diagram of HT-TOFMS is shown as Figure 5. The main difference between HT-TOF and conventional TOF is a modulator is applied to the sample entrance of HT-TOF, and the signal gathered from detector is processed by a multichannel scaler. The

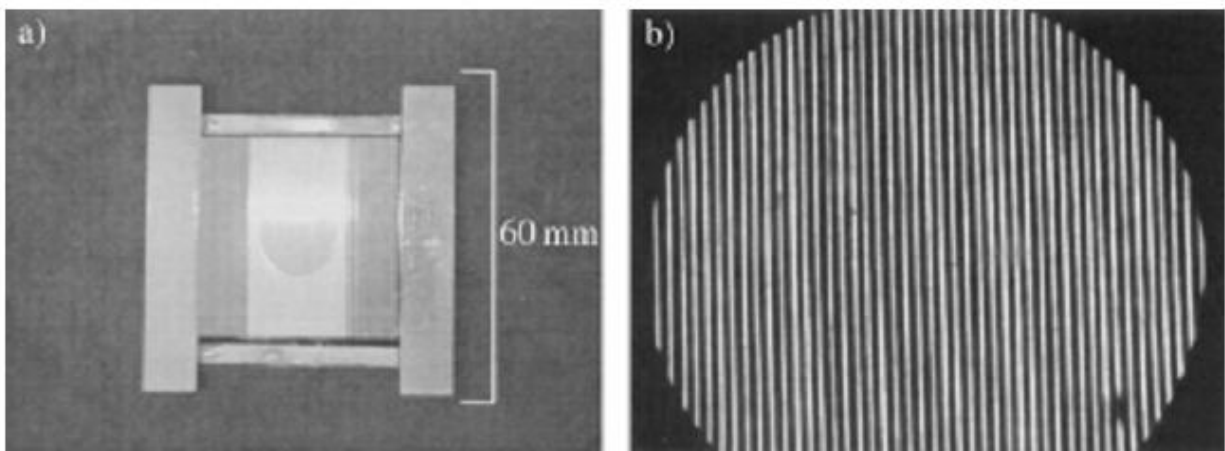


Figure 6. a) Finely spaced Bradbury-Nielsen gate (front view, 100 $\mu$ m spacing) and b) closer view of the optical aperture showing the two interleaved wire sets<sup>26</sup>.

modulator is made by Bradbury-Nielsen gate (BNG) (Figure 6). The idea is to apply a high frequency voltage to alternate wires in a grid, so that ions can only go through at certain times in the voltage phase. The pseudorandom sequence is a Sylvester matrix string, where 0/1 stand for close/open of the BNG.

With Hadamard transform, Fernandez *et al.* coupled TOF with pressurized-capillary electrophoresis<sup>27</sup>. It offers a 50% duty cycle by computer controlled BNG and 16-fold SNR improvement with a 1024-length mask sequence.

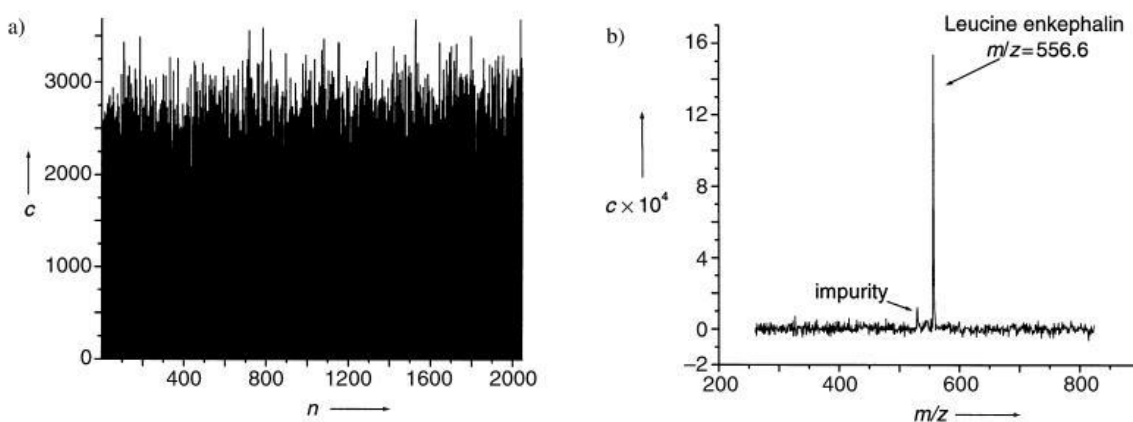


Figure 7. ESI-HT-TOF mass spectrum of 1.4 pmol of the peptide leucine enkephalin ( $1+$ ) dissolved in methanol:water:acetic acid 50:50:1, The acquisition time was 2 s. Diagram a) shows the raw (convoluted) data and b) shows the deconvoluted mass spectrum obtained in low resolution mode. The pseudorandom binary sequence consisted of  $(2^{11} - 1) = 2047$  elements, each of 100 ns duration.  $c = \text{contsm } n = \text{bin number}^{26}$ .

## 2. Hadamard transform capillary electrophoresis (HT-CE)

Electrophoresis is a separation method based on the differential rates of migration of charged species in an applied electric field<sup>28</sup>. It was only performed in paper or porous semisolid gel until in the early 1980s, till scientist began to explore the feasibility of performing electrophoresis in fused silica capillary tubes. Nowadays capillary electrophoresis (CE) is considered as an important tool for many analytical separation problems<sup>29</sup>, especially in DNA sequencing and protein analysis<sup>30</sup>.

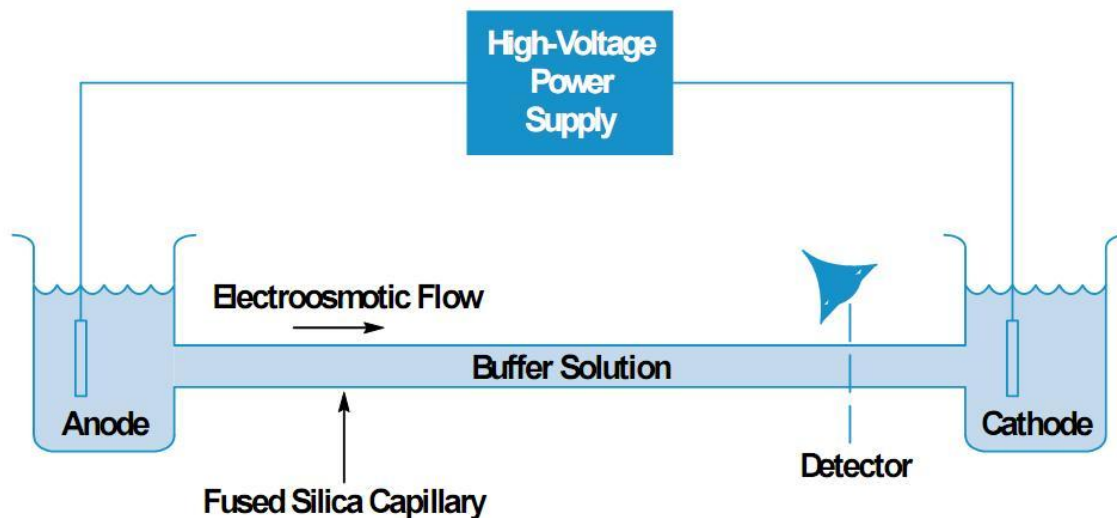


Figure 8. Schematic diagram of free solution capillary electrophoresis<sup>31</sup>.

Despite the wide usage of CE, there is a great limitation of CE: the poor detection limits because of the injection volumes are typically limited to the nanoliter range. There have been some attempts with multiplexing techniques which include cross-correlation electrophoresis<sup>32</sup> and Shah convolution Fourier transform (SCFT) electrophoresis<sup>33</sup>. Kaneta *et al.* demonstrated a multiplexing sample injection technique in CE with Hadamard transform in 1999<sup>11</sup>.

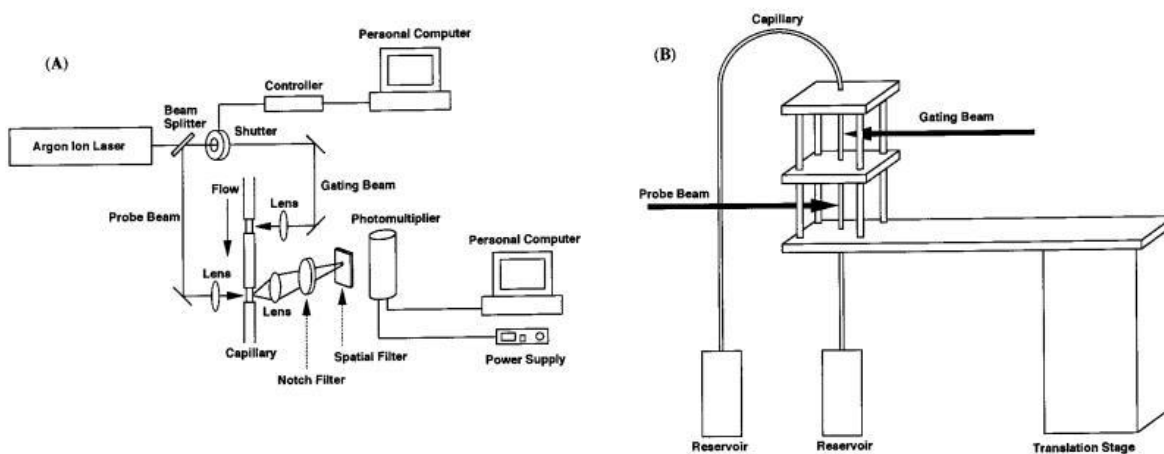


Figure 9. a) Schematic diagram of HT-CE, and b) geometry of capillary<sup>11</sup>.

Multiplexing usually need to modulate the sampling with a pseudorandom sequence. In HT-CE, a laser with computer controlled shutter is used to do the sampling modulation. If the shuttle is open, the fluorescent analyte is decomposed by the strong irradiation with laser, and the

detector will not get the fluorescent signals by laser-induced fluorescence (LIF). If the shuttle is closed, the analyte can generate fluorescent signals when flow through the detector. Figure 9 shows the schematic diagram of HT-CE.

It is easily to observe from Figure 10 that the SNR of the electrophoresis is increased with Hadamard transform. The SNR of original CE is 0.69, showing it is not an acceptable result for quantitative analysis. After Hadamard transform with  $n = 255$  pseudorandom sequence, the SNR is increased to 5.5. Thus an 8-fold improvement in the SNR is obtained by just employing the Hadamard transform.

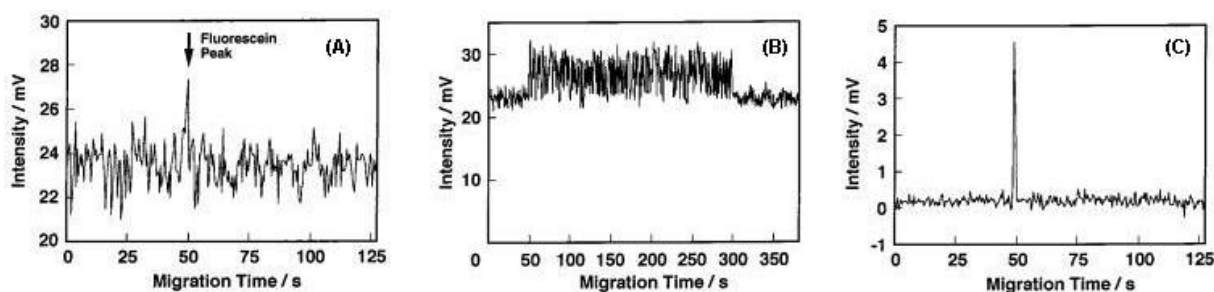


Figure 10. Electropherogram for 10 nmol sodium fluorescein a) of the conventional CE, b) of the raw data by pseudorandom injection and c) after Hadamard transform<sup>11</sup>.

In order to increase the SNR employing the Hadamard transform, work has also been done on increasing the pseudorandom sequence length<sup>34</sup>, using other detector methods (*e.g.* Absorption spectrometry<sup>35</sup>) and other capillary electrophoresis systems (*e.g.* chip-based CE / Microfluidic chip<sup>36</sup>).

## CONCLUSION

Hadamard transform has been applied in analytical chemistry as a chemometrics method to increase the sampling efficiency and signal-to-noise ratio. With low cost and high improvement of SNR, Hadamard transform can be widely applied in many analytical areas.

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