Signal Processing for Biologically Inspired Sensors

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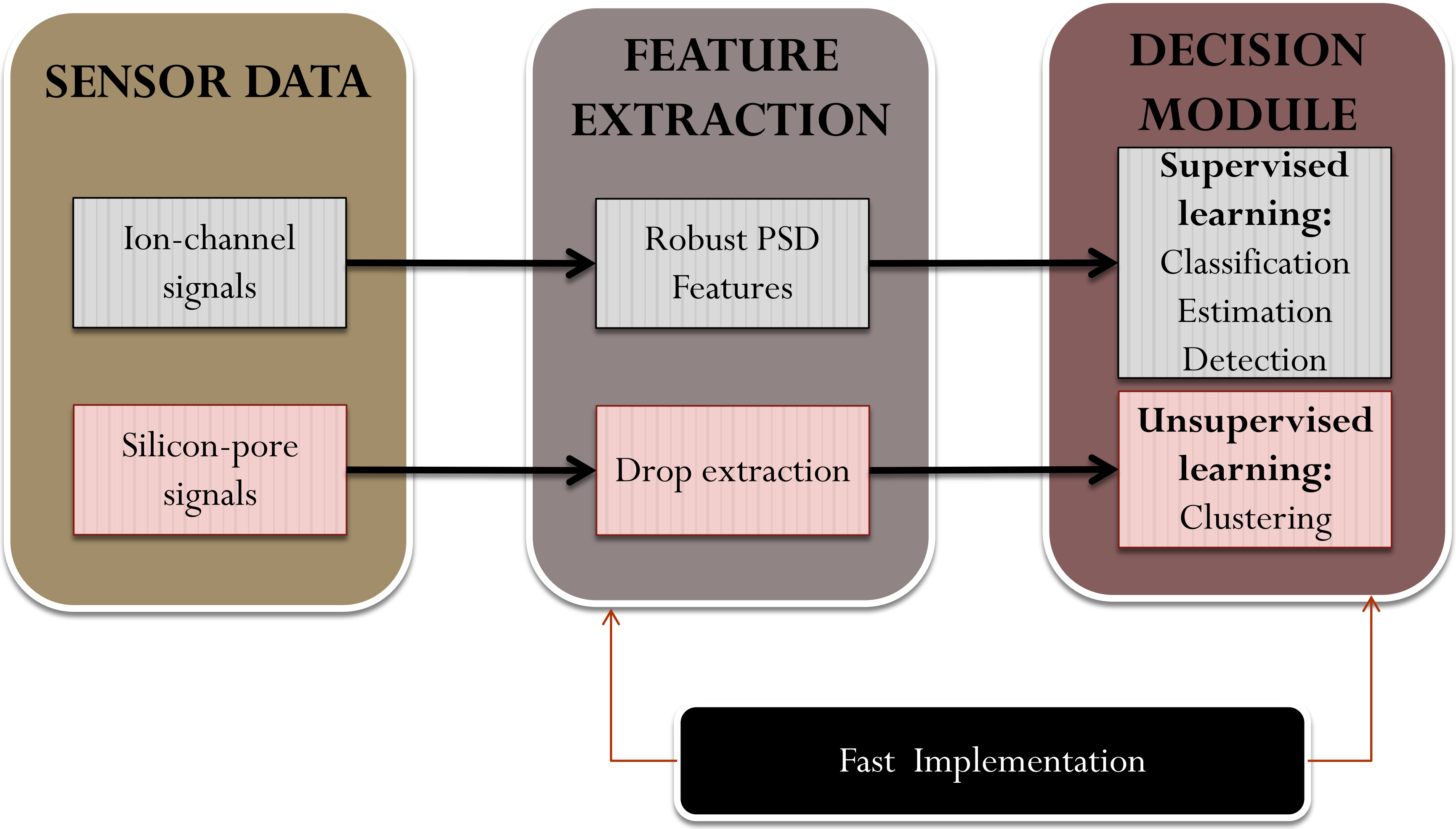
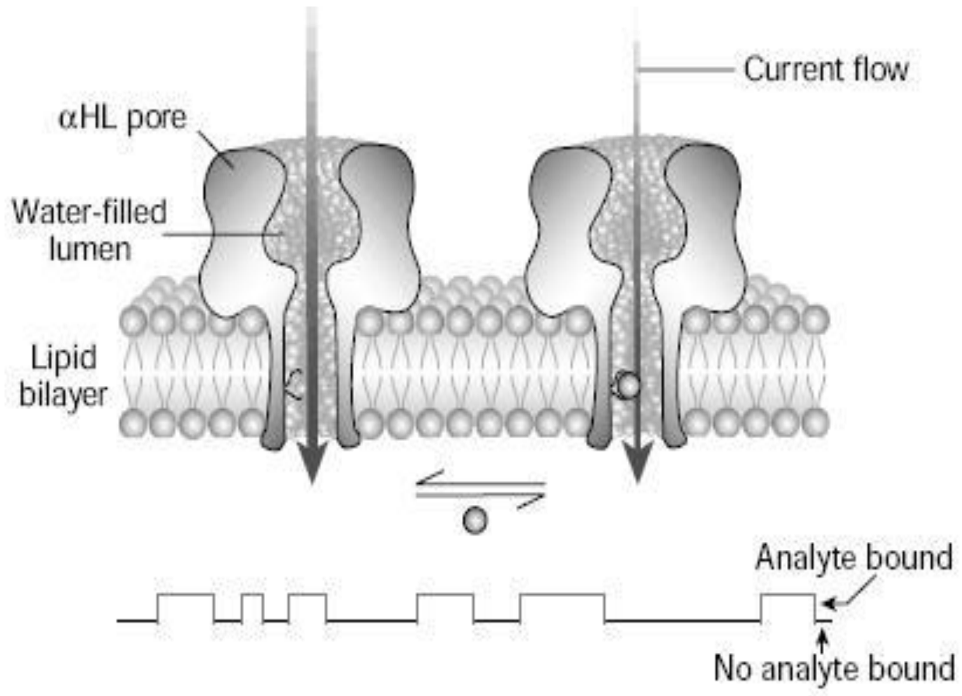
Sensor System



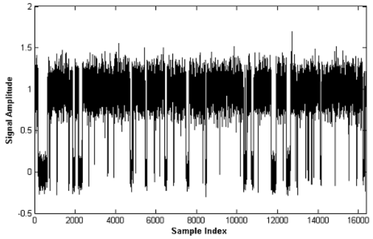
Ion-Channels

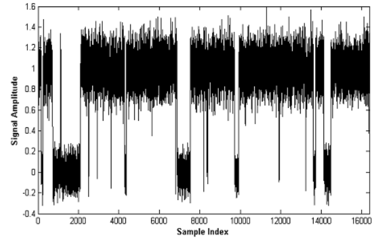
Ion-channels produce a fluctuating current characterized by *binary states*.

An ion-channel can be *characterized* from the magnitude and duration of fluctuations.

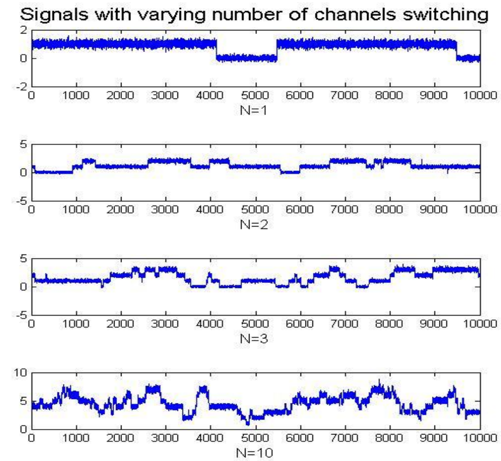


Analysis of Ion-Channel Signals

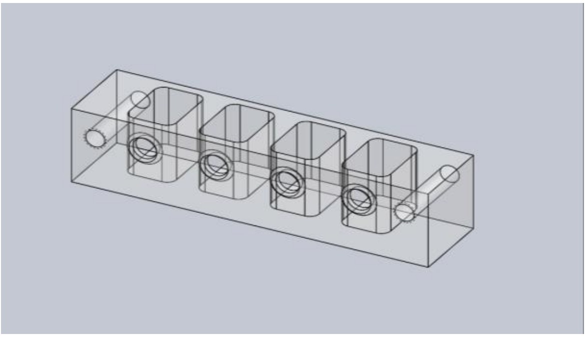




How to **discriminate** between two ion-channels?

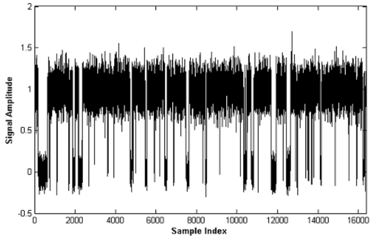


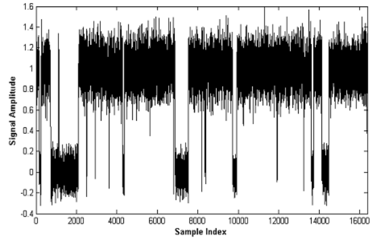
How to **estimate** the number of ion-channels active?



How to detect an **analyte** using the ion-channel sensor array?

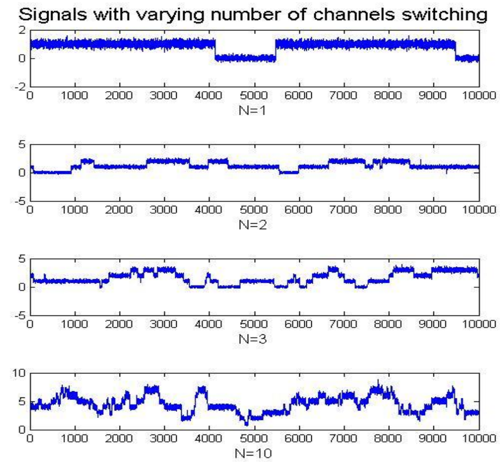
Analysis of Ion-Channel Signals

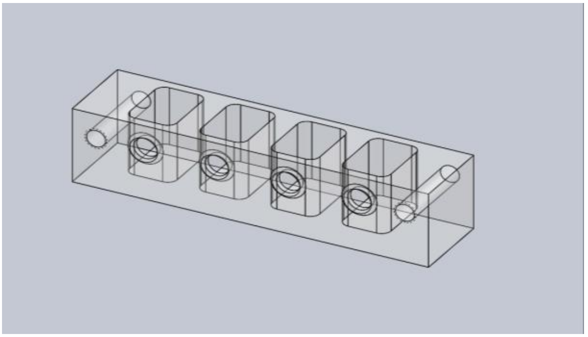




CHANNEL CLASSIFICATION

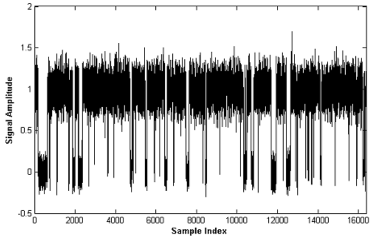
CHANNEL ESTIMATION

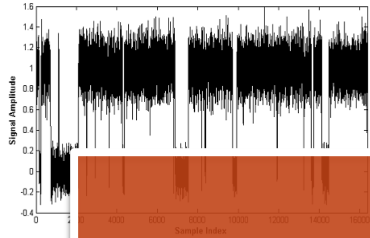




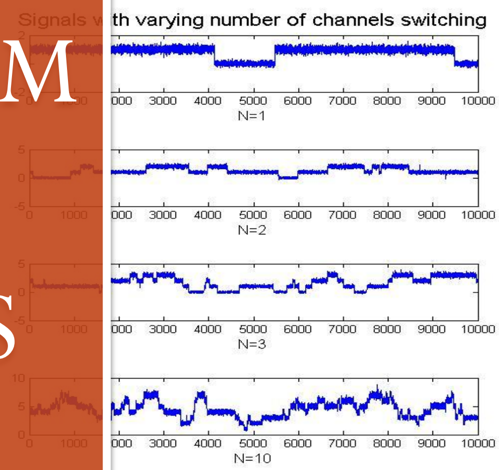
ANALYTE DETECTION

Analysis of Ion-Channel Signals



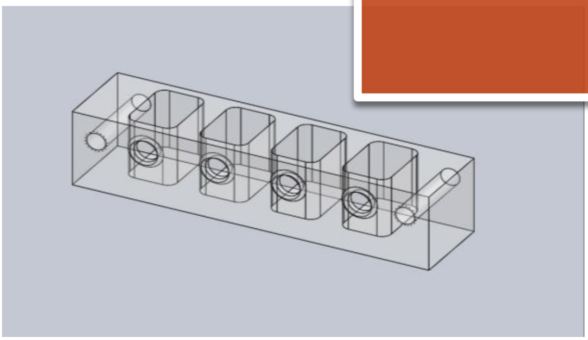


CHANNEL CLASSIFICATION



CHANNEL ESTIMATION

TRANSFORM DOMAIN FEATURES



ANALYTE DETECTION

Feature Extraction - Motivation

- The *PSD* is dependent only on the Eigen decomposition of the *state transition matrix* and it will always exhibit *low-pass characteristics*.

- Proof: Under zero noise conditions, an ideal ion-channel signal is the realization of a *continuous time Markov random* process.
- The continuous time Markov process is defined by the rate transition matrix **Q**, whose rows sum to 0.
- Sampling the process at time intervals **Δ** gives rise to a *discrete time Markov process*. The state transition matrix of the discrete time Markov process is obtained as **A = exp(QΔ)**.

Feature Extraction - Motivation

- Eigen decomposition of state transition matrix:

$$A = U\Gamma U^{-1}$$

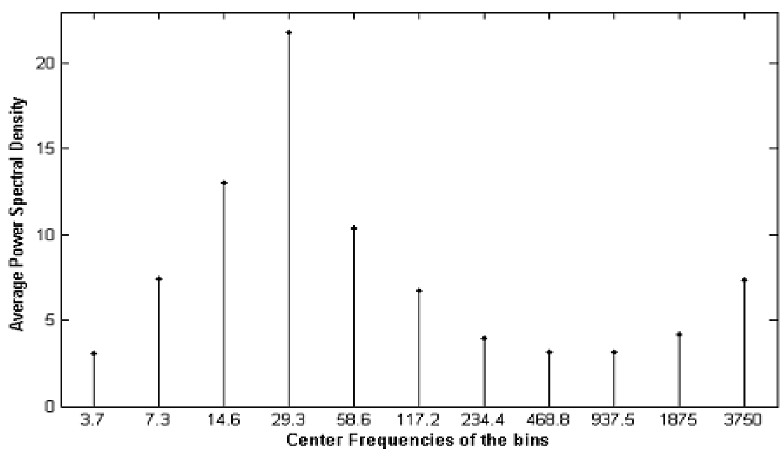
$$PSD : F(z) = s^T P_\pi U\Gamma(z)U^{-1}s$$

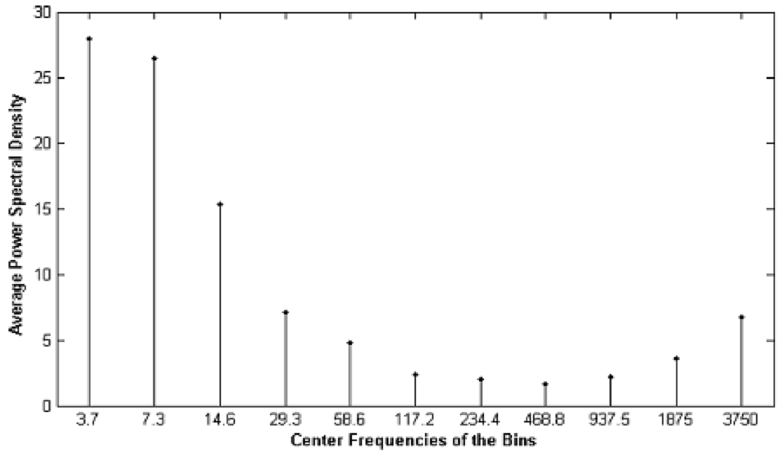
$$\Gamma(z)(i,i) = \frac{(1-\gamma_i^{\ 2})}{[(z-\gamma_i)(z^{-1}-\gamma_i)]}$$

- Here, **s** is the vector of state realizations and P_π contain stationary probabilities.
- This means that the poles of the PSD lie on the positive real axis in the z-plane as γ_i (eigenvalues of **A**) are between 0 and 1.
- Thus, the *PSD* is dependent only on the Eigen decomposition of the *state transition matrix* and it will always exhibit *low-pass characteristics*.

Fourier Domain Features

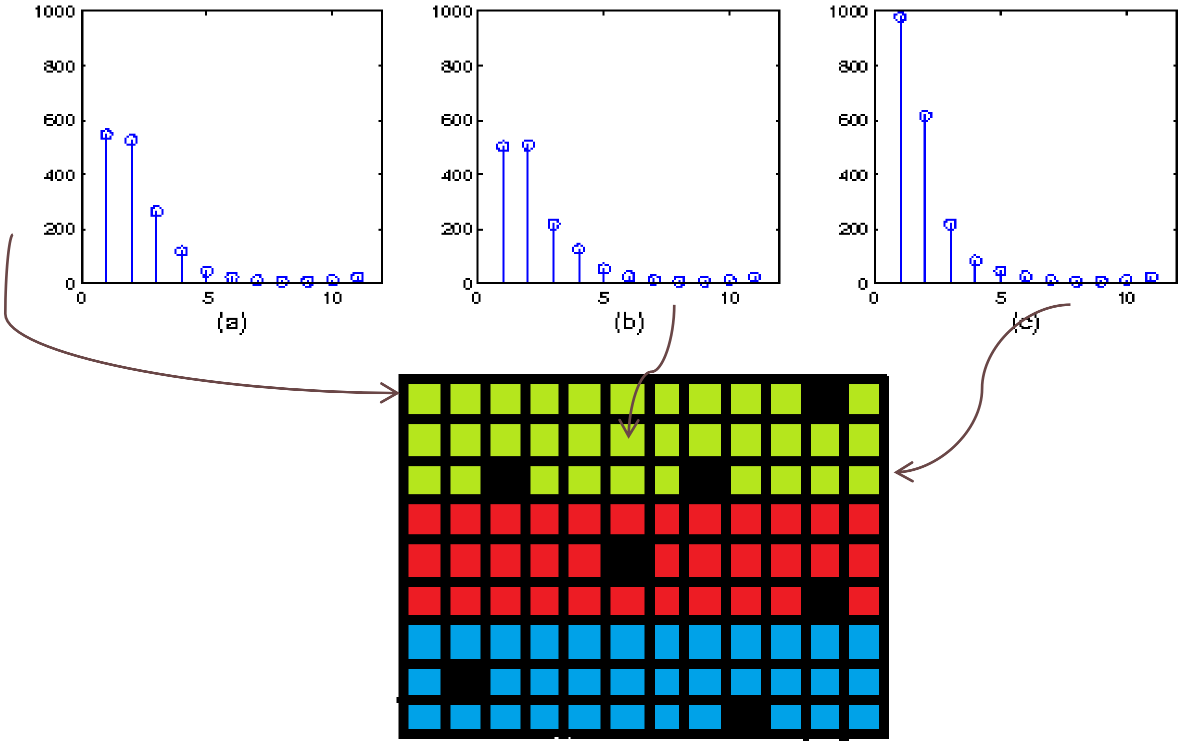
- PSD of the ion-channel signal is obtained using the *Welch procedure*.
- The features are modified PSD.
  - PSD is divided into *dyadic bins.*
  - Values in each bin are *summed and normalized* by the signal power.
- *Lower frequencies* are represented by more points in the feature vector than higher frequencies.



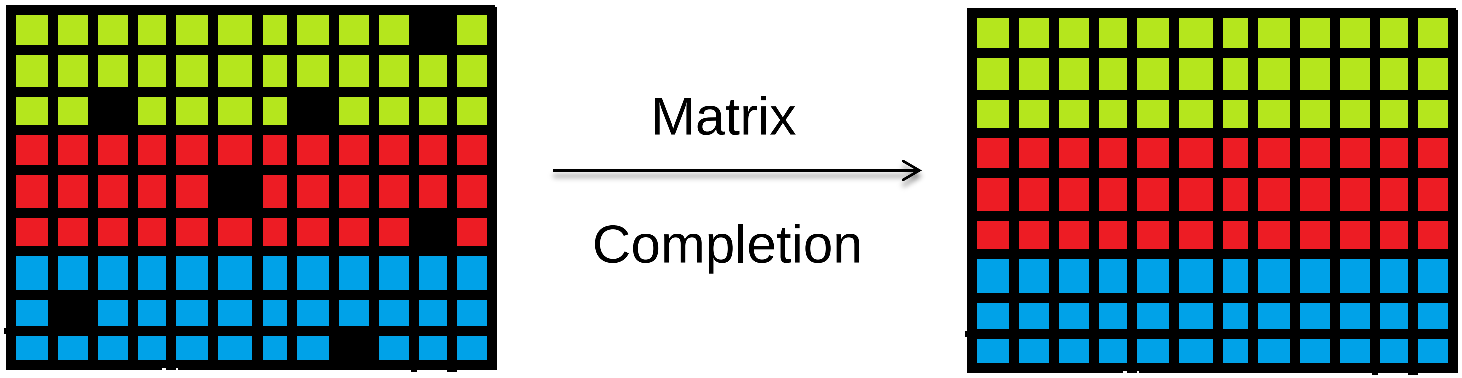


Eliminating Noise in PSD Features

- Noise cannot be modeled.
- Exploit self-similarity between features



Robust PSD Features using Matrix Completion



Eliminate outliers and complete matrix using low rank assumption

Rank Minimization

- Matrix Y can be obtained by solving the following optimization problem

$$\begin{aligned}&\text{minimize } \operatorname{rank}(Y)\\&\text{subject to } P_\Omega(Y) = P_\Omega(M)\end{aligned}$$

- The rank minimization problem is non-convex and NP-hard.
- Rank is replaced by its convex surrogate: nuclear norm

$$\|\mathrm{X}\|_* = \sum_k \sigma_k$$

- The relaxed problem is given by

$$\begin{aligned}&\text{minimize } \|\mathrm{X}\|_*\\&\text{subject to } P_\Omega(X) = P_\Omega(M)\end{aligned}$$

Singular Value Thresholding (SVT)

- Iterative: Prediction and Correction

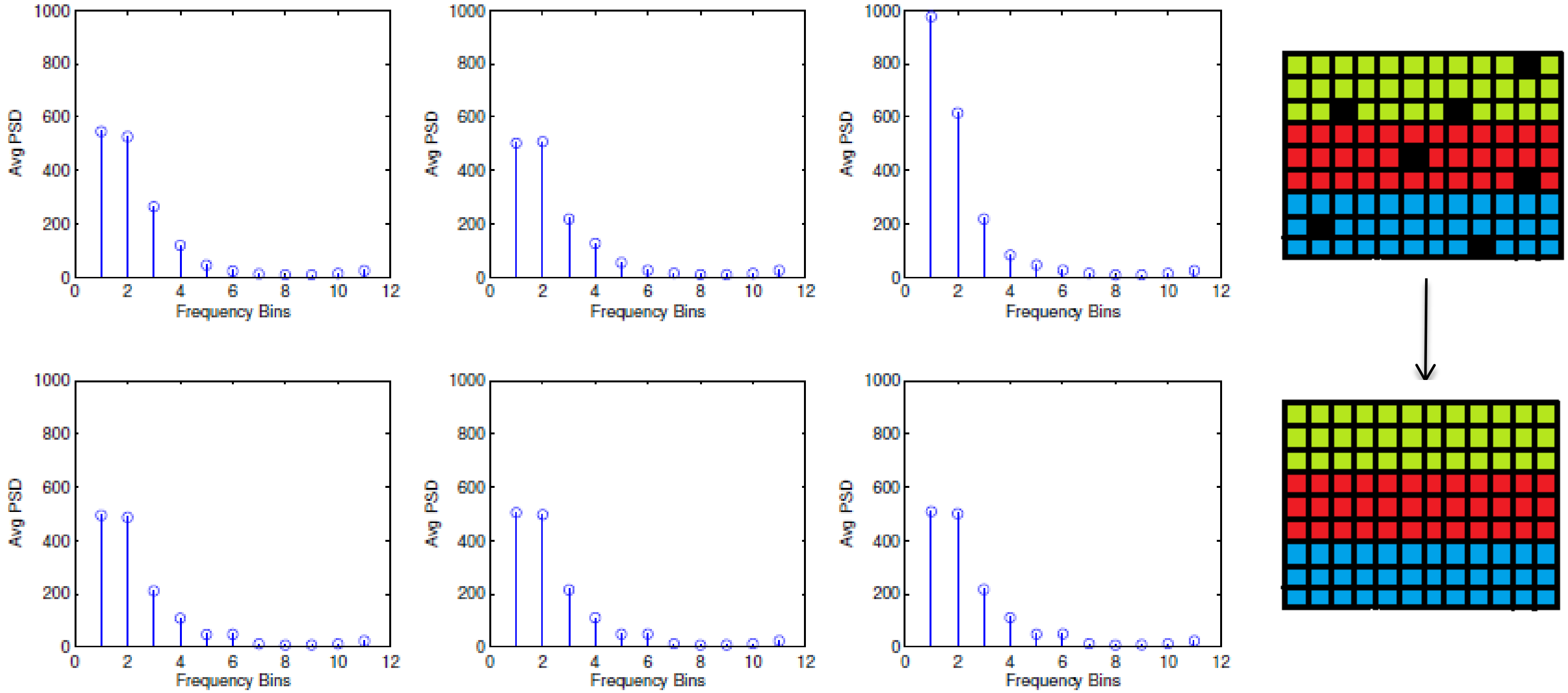
$$Y^k = D_\tau(G^{k-1})$$

$$G^k = G^{k-1} + \delta P_\Omega(M - Y^k)$$

D_τ is the shrinkage operator which retains singular values greater than τ

- Repeated until convergence is achieved.

Proposed Robust PSD Features



Robust PSD features. (a)-(c) are the original PSD features for three segments of the data, while (d)-(f) are the corresponding stabilized PSD features.

Classification Results

TABLE I
CLASSIFICATION PERFORMANCE USING THE ORIGINAL AND STABILIZED PSD FEATURES FOR QUB SIGNALS(LINEAR KERNEL).

Transform Domain	% Classification	% Sensitivity	% Specificity
Original	92.1	91.4	92.8
Stabilized	96.6	98.2	95.1

- Sensitivity and specificity measure the proportion of the correctly identified positives and negatives respectively.
- It can be clearly observed that the post processing of the PSD features leads to improved classification rates.

Estimation of Number of Channels

- **Support Vector regression (SVR**) is used estimate the number of channels from the features of frame each .
- A simple least square fit over the average energy features can give similar results.

Number of Channels	Feature Values	Feature Energy	Feature Value + Energy
N = 1	0.050	**0.033**	0.043
N = 2	0.069	**0.045**	0.063
N = 3	0.034	**0.029**	0.037
N = 10	0.087	**0.071**	0.092

- Table shows the avg. error in the estimates using the three kind of inputs to SVR.

Estimation of Number of Channels

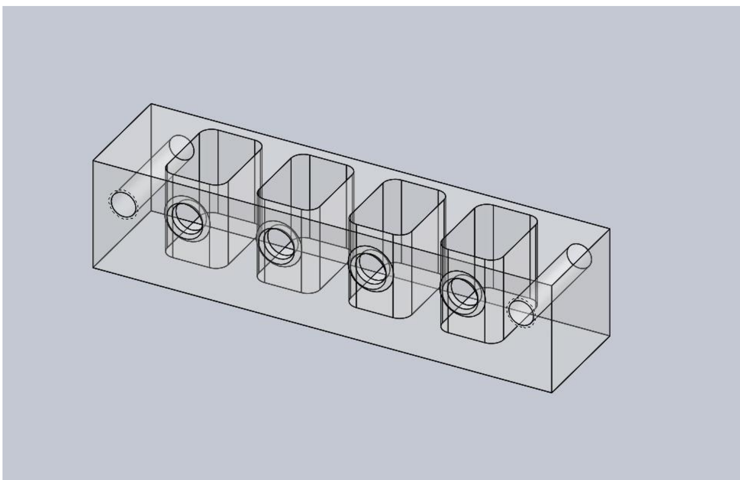
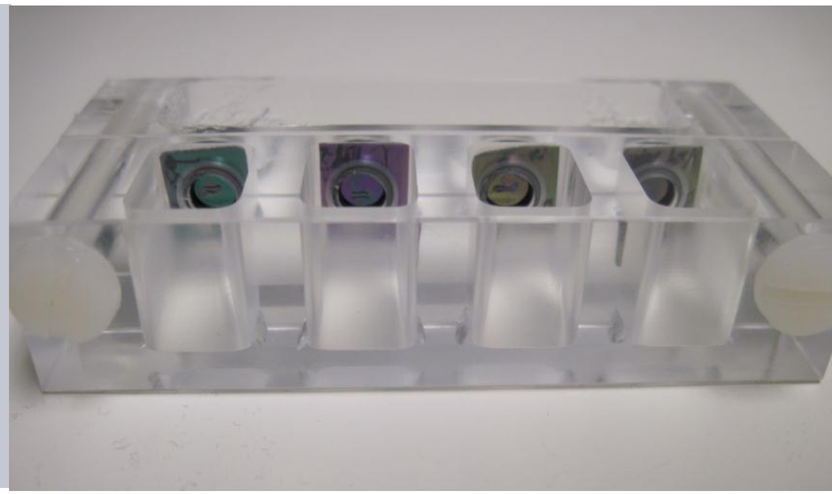
- We observe that dividing the feature vector of a signal frame with N channels operational by N , *normalize* the feature vector in terms of the *energy*.

Number of Channels	Feature Energy – Original	Feature Energy – Normalized
N = 1	407	407
N = 2	1553	383
N = 3	3776	419
N = 10	55850	496

- Normalized Feature Vectors are thus *independent of the number of channels* and are accurate when the SVR is trained for wide range of 'number of channels'.

Sensor Array for Analyte Detection

- *A four sensor array is built*. Three sensors provide the base signals. The other provides the test signal in which analyte is introduced.

- **Analyte Presence Decision**: >10 fold separation in WED w.r.t each base sensor. Simple Voting Scheme for *Decision Fusion* for accurate detection.

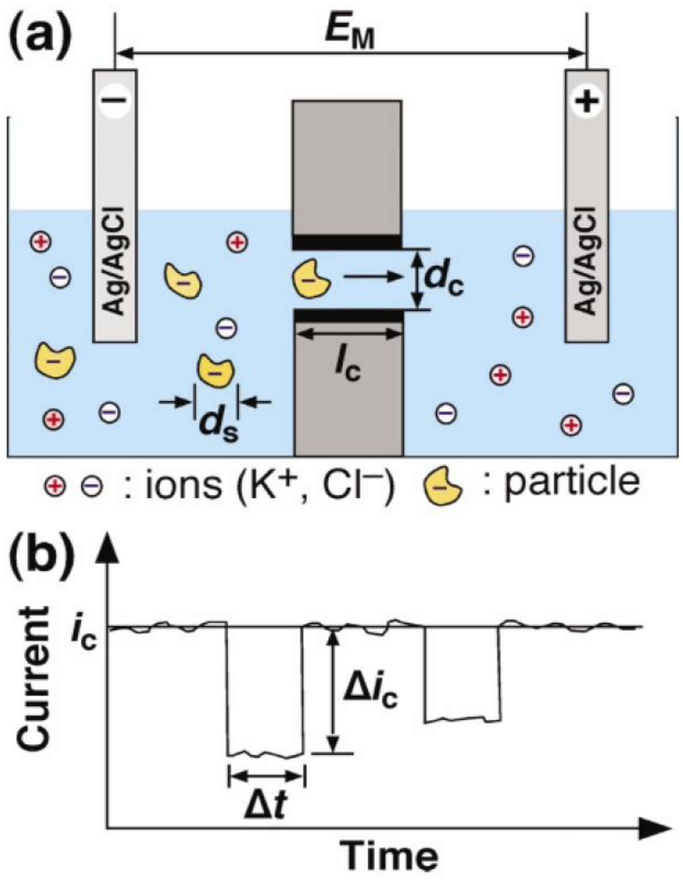
Detection Results

TABLE II
FALSE HITS PERCENTAGE IN DETECTION

Features	Percentage
Original	13.33
Stabilized	1.67

- A detection hit is defined as the case when the WED goes above an empirically obtained threshold. Such cases are referred to as *false hits*.
- Table II shows the percentage of false hits obtained using the original PSD features and the stabilized features.

Silicon Pores as Coulter Counter



R.R. Henriquez et al., Analyst , **129**, 478-482, 2004

A membrane containing a single channel divides two chambers containing an electrolyte solution.

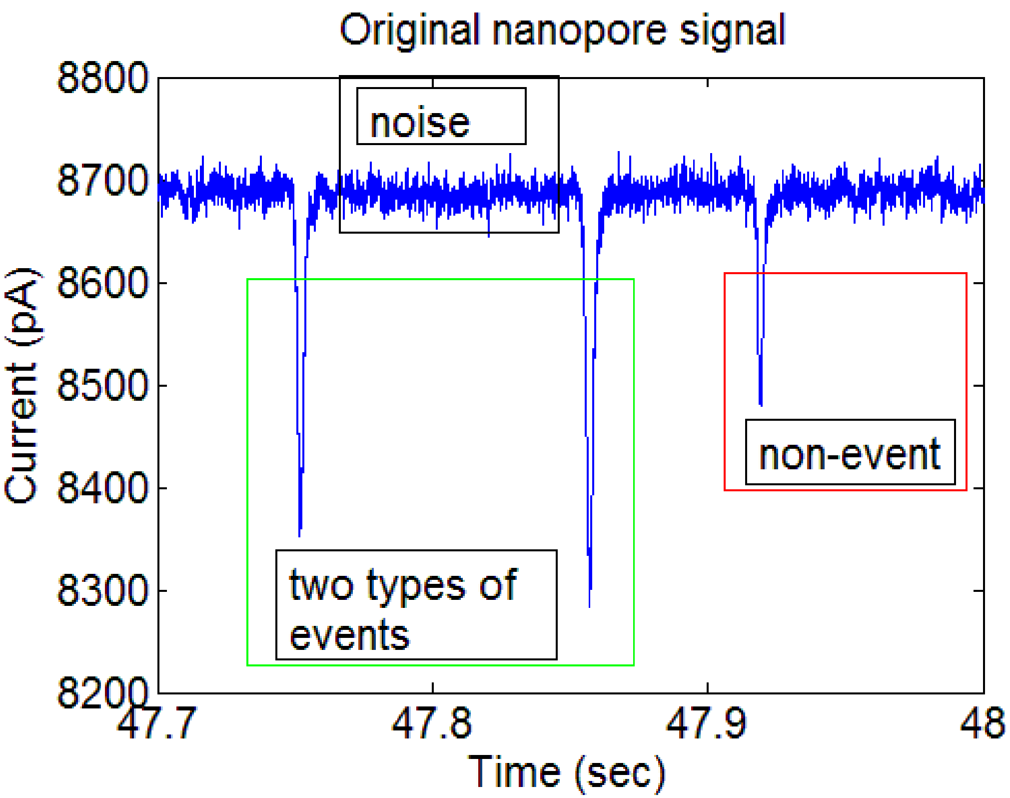
If particles of an appropriate size and charge are present, they will *enter the channel* and *reduce the ion current*.

Coulter counter data consist of a *series of current pulses* associated with the presence of particles within the channel.

Clustering of Events

Motivation:

- Two or more silica beads coagulating : representation of different particles.
- Current drop in case of beads coagulating is unknown.
- Unsupervised learning problem: clustering in the feature domain



Clustering of Events

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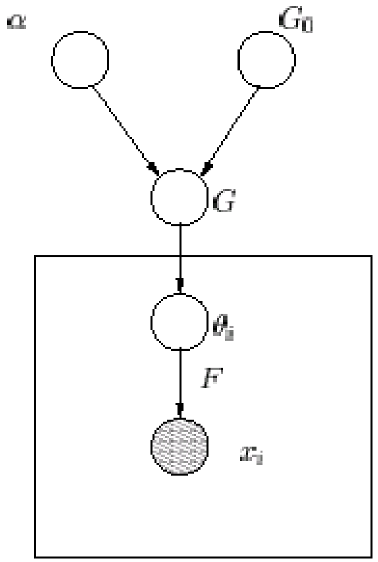
Unknown number of clusters:

- K-means and the mixture of Gaussians: require the number of classes to be known.
- Number of clusters: Dirichlet mixture model, Minimum Description Length (MDL) Principle.
- Spectral Clustering: Similarity based clustering scheme.

Graphical Model for DPMM

DP Mixtures

$$x_i \mid \theta_i \sim F(\theta_i)$$
$$\theta_i \mid G \sim G$$
$$G \sim DP(\alpha, G_0)$$



If F is a normal distribution, this is the a Gaussian mixture model. Gibbs Sampling is used to find the marginals.

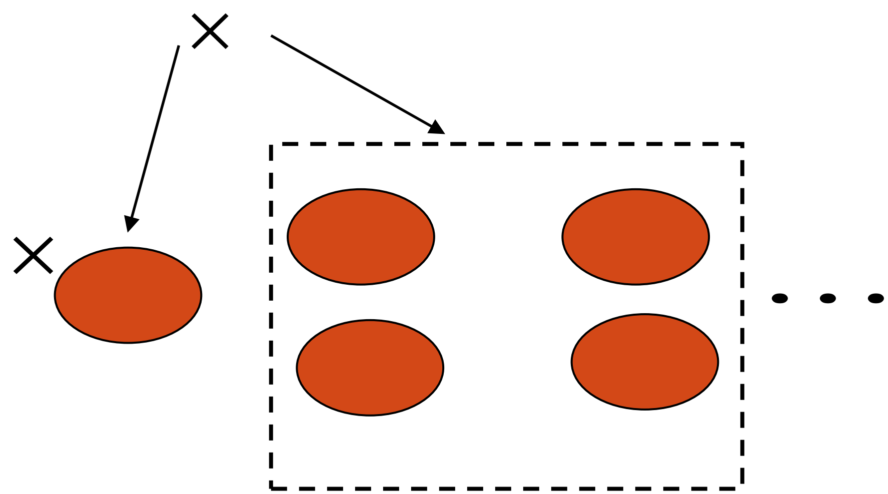
Chinese Restaurant Process

Chinese Restaurant Process is an interpretation of DPMMs or Infinite Mixture Models. It explains the ability to form new clusters.

Unlimited number of tables

Each table has an unlimited capacity to seat customers.

The (m+1)th subsequent customer sits at a table drawn from the following distribution:



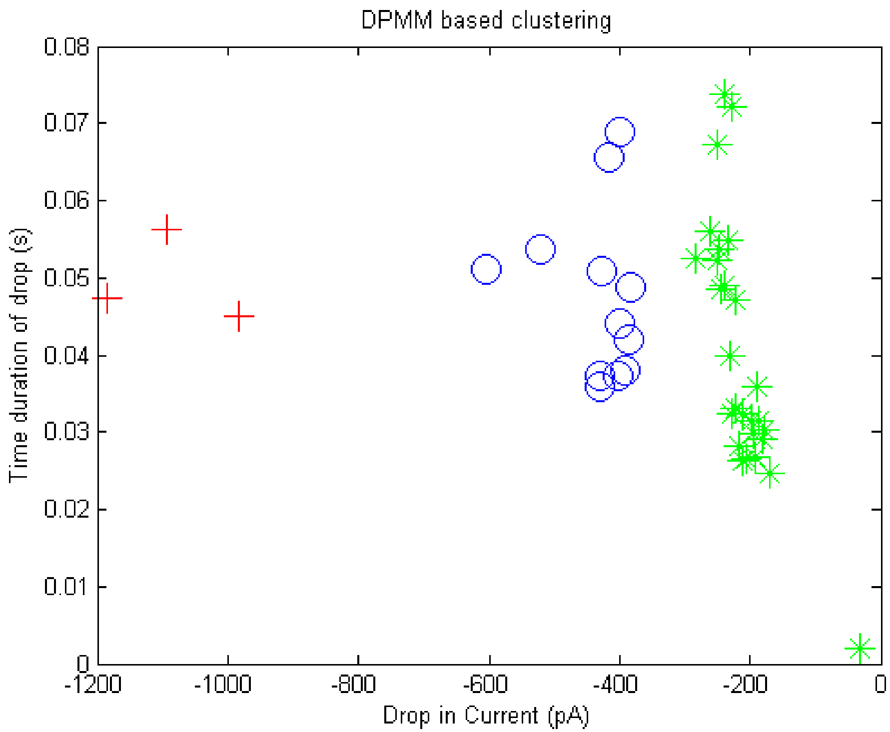
$$p(occupied\ \ table\ i\,|\,previous\ customers) = \frac{m_i}{\alpha + m}$$

$$p(an\ unoccupied\ \ table\,|\,previous\ customers) = \frac{\alpha}{\alpha + m}$$

where m_i is the number of previous customers at table *i* and α is a parameter.

Clustering Results

- Dataset 1: 1523 drops and 43 events
- Levels of wavelet decomposition: 5.
- DPMM concentration parameter α was chosen to be 2.



- The mean drop amplitudes obtained for the three clusters are -213.4 pA, -433.0pA and -1086.7 pA .

Normalized Spectral Clustering

Number of clusters
MDL principle: The best hypothesis for a given set of data is the one that leads to the *best compression* of the data.

Similarity based clustering
Algorithms that *cluster points using eigenvectors* of matrices derived from the data. These are inherently based on similarity between data points.

Do not assume *generative model* hence can work for *different shapes* of clusters.

We use a normalized spectral clustering approach proposed by Ng et al. Uses k Eigenvectors simultaneously and computes directly a *k way partition*.

Spectral Clustering Algorithm

- Given a set of points

$$S = \{s_1, s_2, \ldots, s_k]$$

- Form the affinity matrix

$$A_{ij} = e^{-\|s_i - s_j\|^2 / 2\sigma^2} \quad i \neq j \quad A_{ii} = 0$$

- Define diagonal matrix

$$D_{ii} = \sum_k a_{ik}$$

- Form the matrix L:

$$L = D^{-1/2} A D^{-1/2}$$

- Stack the k largest eigenvectors of L to form the columns of the new matrix X:

$$X = [x_1, x_2, \ldots, x_k]$$

- Renormalize each of X’s rows to have unit length. Cluster rows of X as points in R^k which is reflecting on S.

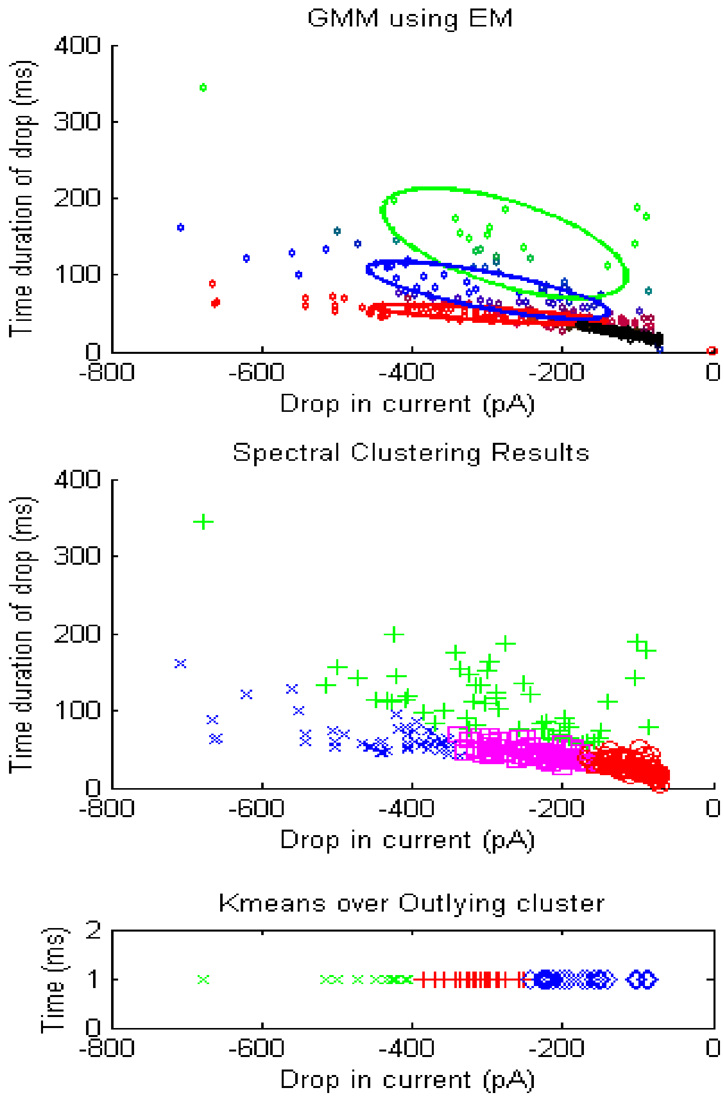
Clustering Results

Two-fold clustering:
Spectral clustering using both time and amplitude and identify the outliers;.
Kmeans on the outlying cluster using only the current drop feature.

MDL estimate: number of clusters: 4

GMM with EM: does not provide meaningful clusters.

Spectral clustering: three natural clusters and an outlying cluster consisting of events of high time duration.



Conclusions

- Wavelet based *de-noising* was demonstrated on silicon-pore signals.
- Algorithm for *extracting and clustering events* in silicon-pore signals were implemented.
- *Transform domain features* feature were proposed to characterize ion-channel signals.
- Robust PSD features obtained with *low rank* assumption lead to higher classification rates.
- PSD features were also used in *SVR* setup to estimate number of channels.
- *Decision level fusion* of ion-channel sensor array produced lower false hit rates.

Future Work

Ion-channel signals

- Develop feature level fusion algorithm for multiple sensors.

Silicon-pore signals

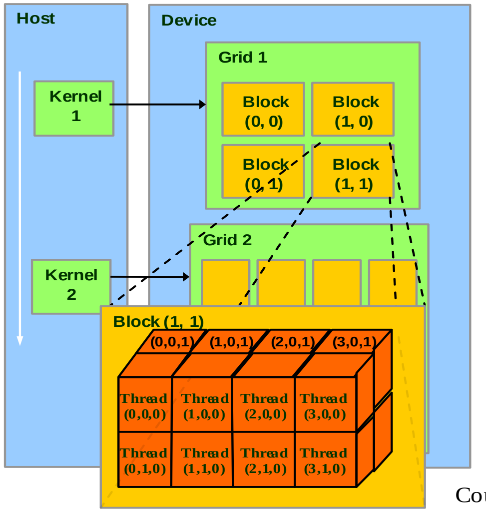
- Sparse decomposition of signal for accurate event detection.
- Modify spectral clustering (of events) for automatic order selection.

Implementations

- Speed up heavy computations using Graphics Processing Unit.

GPU for Ion-channel / Silicon-pore Signals

- We plan to extend the implementation to *wavelet based de-noising*.
- Among the unsupervised learning algorithms Bayesian Clustering is prime candidate for parallelization. These algorithm involve *Markov Chain Monte Carlo (MCMC)* estimations which are computationally intensive but highly independent
- *Matrix completion* on GPU by parallelizing matrix computations.



Courtesy: NDVIA

Publications

Journal Publications

[1] K. N. Ramamurthy, J. J. Thiagarajan, P. Sattigeri, M. Goryll, A. Spanias, T. Thornton, S.Phillips, Transform domain features for ion-channel signal classification*. Biomedical Signal Processing and Control*, 6(3), 219-224, 2010. Elsevier Ltd.

Conference Proceedings

[2] B. Konnanath, P. Sattigeri, T. Mathew, A. Spanias, S. Prasad, M. Goryll, T. Thornton and P. Knee, "Acquiring and Classifying Signals from Nanopores and Ion-Channels ," *IEEE ICANN 2009*, Limassol, September 2009.

[3] K. N. Ramamurthy, J. J. Thiagarajan, P. Sattigeri, B. Konnanath, A. Spanias, T. Thornton, S. Prasad, M. Goryll, S.Phillips and S. Goodnick, "Transform Domain Features for Ion-Channel Signal Classification using Support Vector Machines", *in 9th International Conference on Information Technology and Applications in Biomedicine*, (ITAB-09'), Larnaca, November 2009.

[4] P. Sattigeri, J. J. Thiagarajan, K. N. Ramamurthy, B. Konnanath, T. Mathew, A. Spanias, M. Goryll, T. Thornton, S. Prasad, S. Phillips, "Signal processing for biologically inspired sensors*," 4th International Symposium on Communications, Control and Signal Processing* (ISCCSP), 2010, vol., no., pp.1-5, 3-5 March 2010.

[5] P. Sattigeri, J. J. Thiagarajan, K. N. Ramamurthy, P. Joshi, A. Spanias, M. Goryll and T. Thornton, "Analysis of Coulter counting data from nanopores using clustering," in *Sensor Signal Processing for Defence* (SSPD), London, UK, 29-30 September 2010.

[6] P. Sattigeri, J. J. Thiagarajan, K. N. Ramamurthy, P. Joshi, A. Spanias, M. Goryll and T. Thornton, "Analyte detection using an ion-channel sensor array," in 16th international conference on *Digital Signal Processing* (DSP2011), Corfu, Greece, 6-8 July 2011.

[7] P. Sattigeri, J. J. Thiagarajan, K. N. Ramamurthy, A. Spanias, M. Goryll and T. Thornton, "Robust PSD features for ion-channel signals," in *Sensor Signal Processing for Defence* (SSPD), London, UK, 29-30 September 2011.

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