Barker-Coded Node-Pore Resistive Pulse Sensing with Built-in Coincidence Correction

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Introduction

Background

- The resistive-pulse technique [1][2] (i.e. the Coulter-counter technique [3]) is widely employed in many fields to estimate the parameters of single particles, e.g. cells or microspheres, as they are manipulated by or as they interact with a microfluidic channel. Several areas of application are cell biology [4], clinical medicine [5], and pathogen detection [6][7]).
- Most applications require a high-throughput screening of particles to be of practical use.
- Pathogen detection applications rely on channel-particle interactions and these interactions can be further emphasized with longer channels.

The Problem

- A high-throughput of particles flowing through a long microfluidic channel results in multiple particles transiting the channel simultaneously (coincidence event). For many applications coincidence data is considered uninterpretable and is the limiting aspect of the device.

Our *Computational Sensing* Solution

- Encode the channel's impulse response with a modified Barker code [8].
- Resolve coincidence corrections by posing and solving a sparse deconvolution with a modified successive interference cancellation algorithm [9].

Node-Pore Sensing & Barker Coding Overview

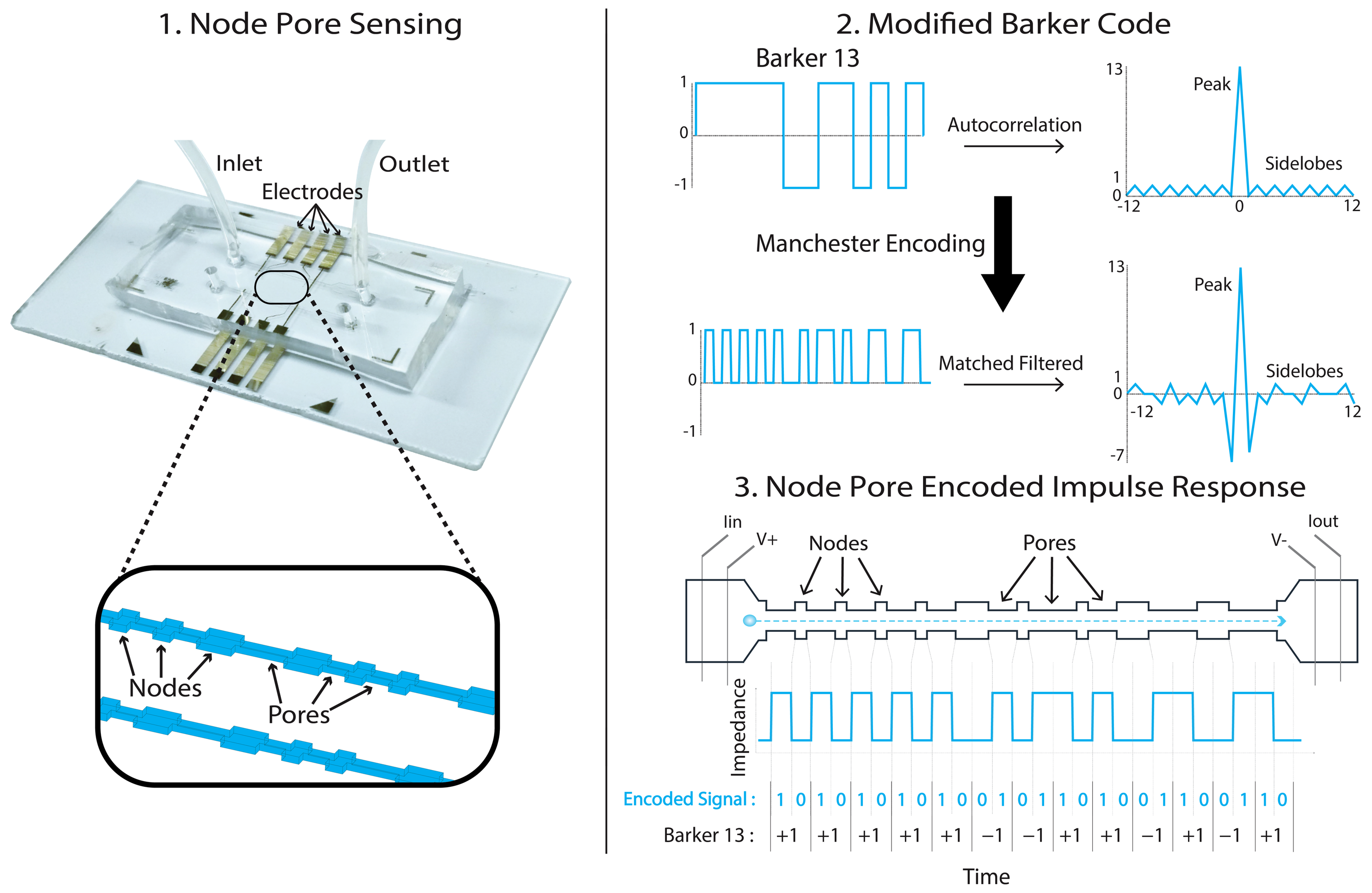

Fig 1. Microfluidic Node-Pore Sensing & Modified Barker Code Overview: (1) Polydimethylsiloxane channel modulated with wider (Nodes) and narrower (Pores) regions bonded to glass substrate with four-probe sensor, (2) Pulse compression properties of our modified Barker-13 encoding, (3) Node-Pore encoding schematic and impedance response of our modified Barker-13 encoded microfluidic channel.

System Modeling

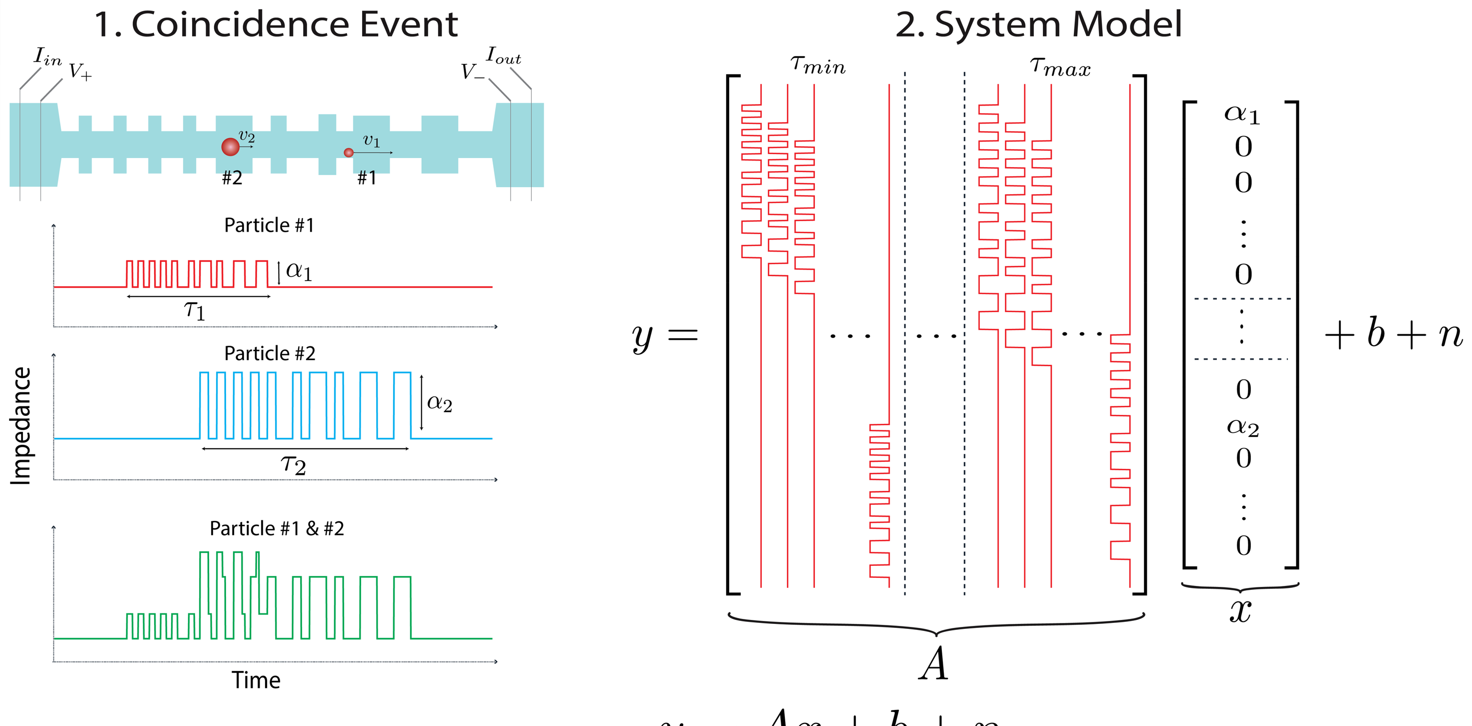

Fig 2. Coincidence Events & System Modeling: (1) Coincidence event response is the linear combination of the individual impulse responses, parametric with arrival-time, transit-time, and particle size, (2) System model with a special transit-time dependent convolutional model (A), sparse amplitude vector indexing into convolutional model (x), affine slow-varying baseline (b), and noise term (n).

$$y = Ax + b + n$$

A: Transit-time Dependent Convolution
x: Sparse Particle Vector
b: Smooth Time-varying Baseline
n: Gaussian Noise
y: Measured Data

Sparse Deconvolution

$$\min_{x,b} \quad ||Ax + b - y||_2^2 + \lambda ||Db||_2^2$$
$$\text{s.t.} \quad \text{cardinality}\{x \in range(t, \tau)\} < k$$

A: Transit-time Dependent Convolution
x: Sparse Particle Vector
D: Second Difference Matrix (to penalize baseline)
b: Smooth Time-varying Baseline
n: Gaussian Noise
y: Measured Data
τ: Transit-Time Parameter
t: Arrival-Time Parameter
k: Sparsity Level

Modified Successive Interference Cancellation Solution

1. Apply matched filterbank
2. Adaptive signal component detection
3. Fit detected signal model components to data

$$\min_{\tilde{x},b} \|\tilde{A}_i \tilde{x}_i + b - y\|_2^2 + \lambda \|Db\|_2^2$$

4. Signal cancellation

Successive Interference Cancellation

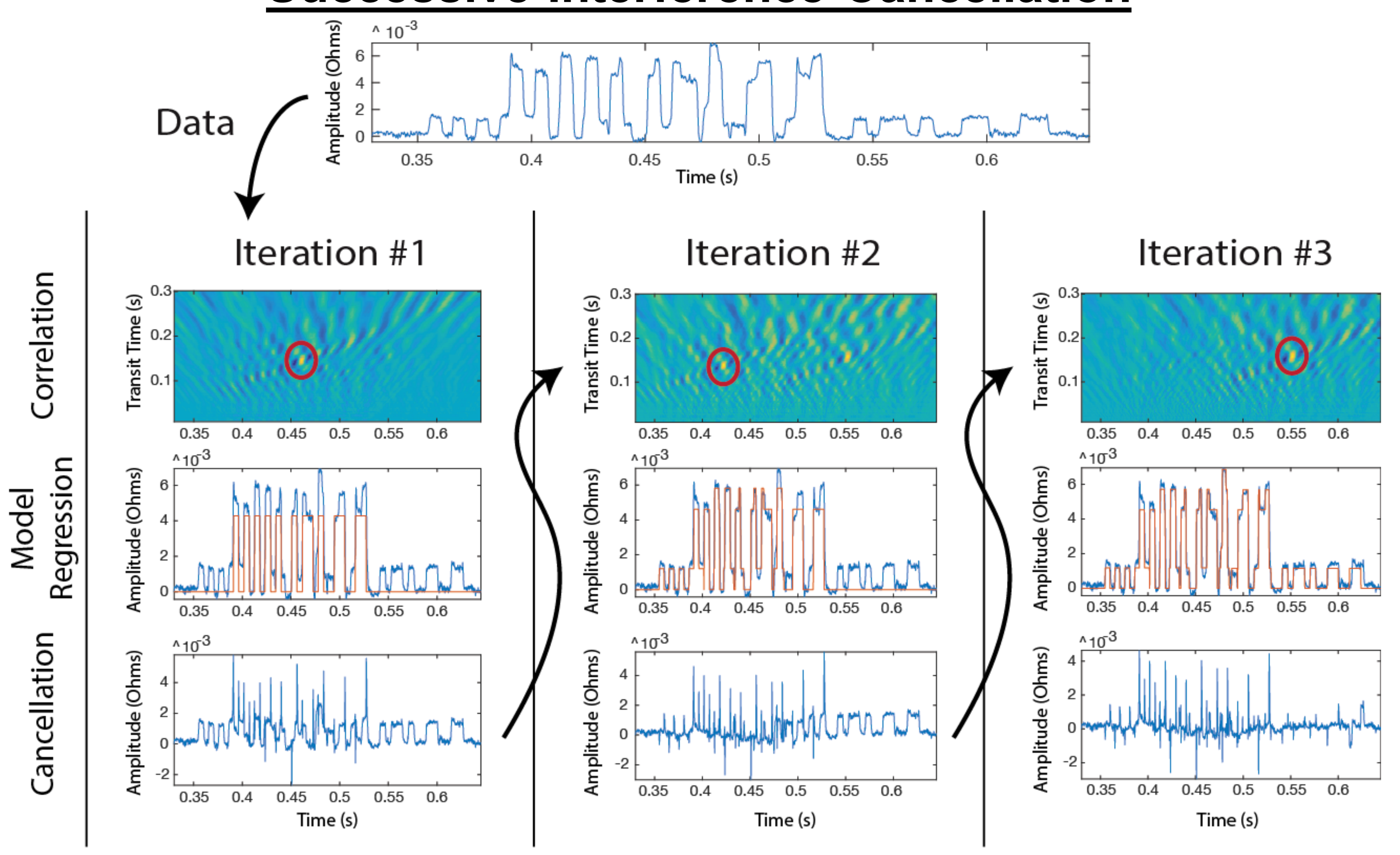

Fig 3. Successive Interference Cancellation Iterations: Application of three iterations of our modified successive cancellation algorithm to experimental data: Correlation with matched filterbank, Detection of signal components (red circles), Pruned model regression, Signal interference cancellation.

Model Error

Global Model Error

- Manufacturing error causes global mismatch from the ideal system model
- Mitigated by a calibration setup where the true geometry of the channel is regressed from the inter-pulse timings of high-SNR responses

Stochastic Model Error

- Stochastic flow fluctuation causes random variations from the ideal system model leading to sparse outlier residuals and biased least-square amplitude estimates
- Bias is reduced by estimating amplitude with a robust regression (placing an l1-norm on the data consistency)
- Robust regression solved via iterative reweighted least-squares [10]

$$\min_{\tilde{x},b} \|W(\tilde{A}\tilde{x} + b - y)\|_2^2 + \lambda \|Db\|_2^2$$
$$\text{where,} \quad W_{(j,j)} = \frac{1}{|\tilde{A}_{(j)}\tilde{x} + b_{(j)} - y_{(j)}|}$$

Experimental Results

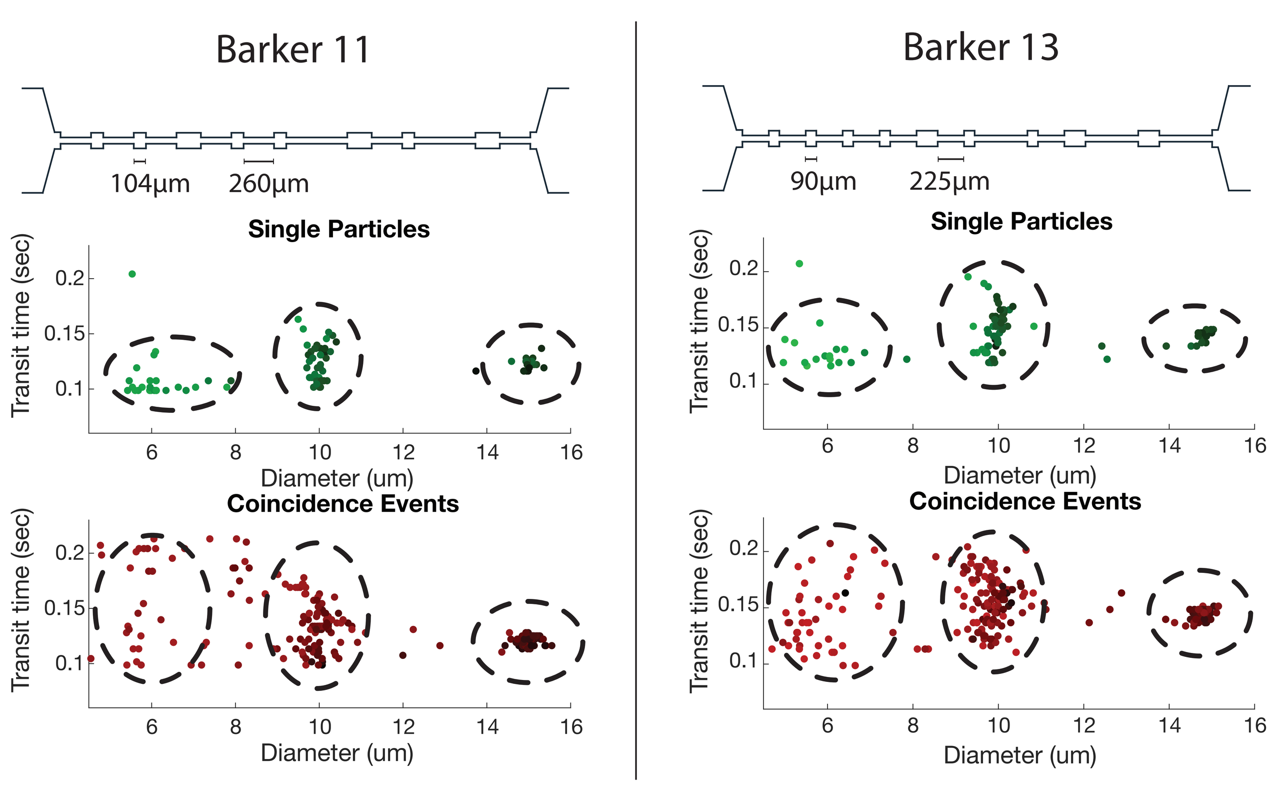

Fig 4. Particle Size vs. Transit-Time Experimental Results: We screened a 1:1:1 ratio of 5μm, 10μm, and 15μm diameter polystyrene microspheres at a concentration of 5 x10[5] particles/mL through devices encoded with the modified Barker-11 and with the modified Barker-13. Experimental data was coincidence corrected with proposed sparse deconvolution and was solved with our proposed iterative method. Transit time (s) versus particle size (um) is plotted, where each detected particle is highlighted with intensity corresponding to the correlation peak to estimated side-lobe ratio (darker – more reliable, lighter – less reliable).

Discussion

	Short Channel	Long Channel	m-B13 Encoded
Applications	✗	✓	✓
Coincidence Prone	✓	✗	✓
Dynamic Range	✓	✓	✓
Temporal Resolution	✓	✗	✓

- The energy of sparse outlier residuals is spread in the correlation domain effectively decreasing the signal to noise + interference ratio (SNIR) of particles in successive iterations.
  - Coincidence events can lead to false alarms and missed detections due to decreased SNIR.
- The trade off between false alarms and missed detections should be examined for single particle and coincidence settings so detection thresholds can be selected adaptively to avoid detection errors.

Conclusion

- Long microfluidic channels can be encode with a modified Barker code arrangement of nodes and pores.
- Our modified deconvolution method exploits the pulse compression properties of Barker codes to resolve coincidences.
- System model calibration and robust regression reduce detection and estimation errors due to global and stochastic system model error.

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