Ben-Gurion University of the Negev

ISOEN

Electrochemical biosensor fundamentals for artificial olfaction and taste

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NanoBioElectronics Laboratory

Ben-Gurion University of the Negev

The Ben-Gurion University of the Negev, Israel

David Ben-Gurion: the 1st prime minister of Israel (1886 – 1973)

Ben-Gurion University of the Negev

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Prof. Janina Bahnemann (U. of Augsburg)
Prof. Umut Gurkan (CWRU)
Prof. Joel Voldman (MIT)
Prof. Rong Fan (Yale)

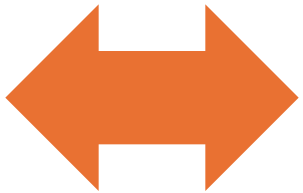
A long-standing gap between two adjacent communities

WHAT THE E-NOSE COMMUNITY KNOWS

Pattern-recognition depth

- Drift compensation in MOS arrays
- Calibration transfer across instruments
- Ensemble classifiers, decades of benchmarks

Cross-pollination zone



WHAT ECHEM BRINGS

Chemical & transduction depth

- Rich voltammetric signatures (CV, DPV, SWV, EIS)
- Redox-mechanism specificity
- In vivo / in-fluid deployment

The algorithmic layer is where the two communities can most help each other

Where do you feel the most pain right now?

Pick the pillar that costs you the most time or sleep right now.

Selectivity — telling target from interferent

Calibration — recalibrating sensors keeps eating my time

Drift — performance falls off after deployment

Biofouling — biological media destroy the signal

Vote on Mentimeter — code below.

Mentimeter

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The four algorithmic pillars

AGENDA

1 Selectivity 12 min

Overlapping redox peaks → algorithmic problem

- **NBEL anchor: dopamine vs. norephinephrine**

PCA · PLS-DA · SVM · (DL when N is large)

2 Calibration 12 min

Electrode-to-electrode variability + matrix shift

- **NBEL anchor: microelectrode arrays**

Univariate · PLSR · Calibration transfer · DL transfer

3 Drift 12 min

Four superimposed sources — and sometimes the signal

- **NBEL anchor: MEMIC biofilm platform**

Explicit correction · drift modeling · domain adaptation

4 Biofouling 12 min

Upstream of the other three — detect, then gate

- **NBEL anchor: MEMIC biofilm platform**

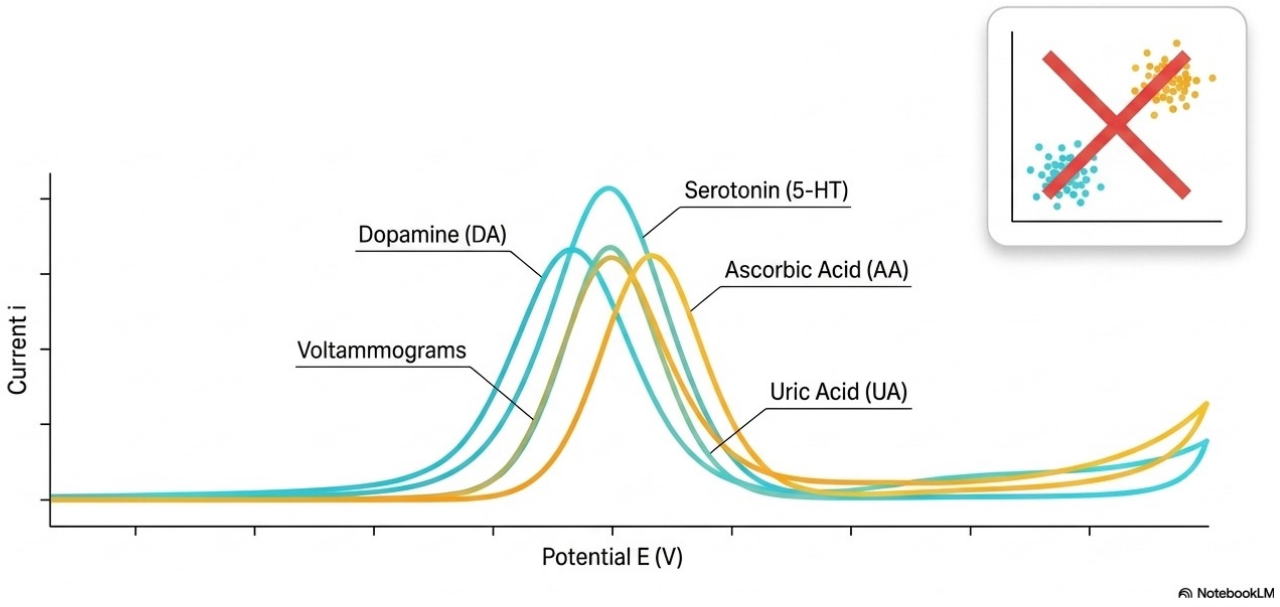
EIS features · one-class anomaly · fusion gating

failure modes (3 min) · hands on (5 min) · synthesis & close (4 min)

Why ECHEM selectivity is different

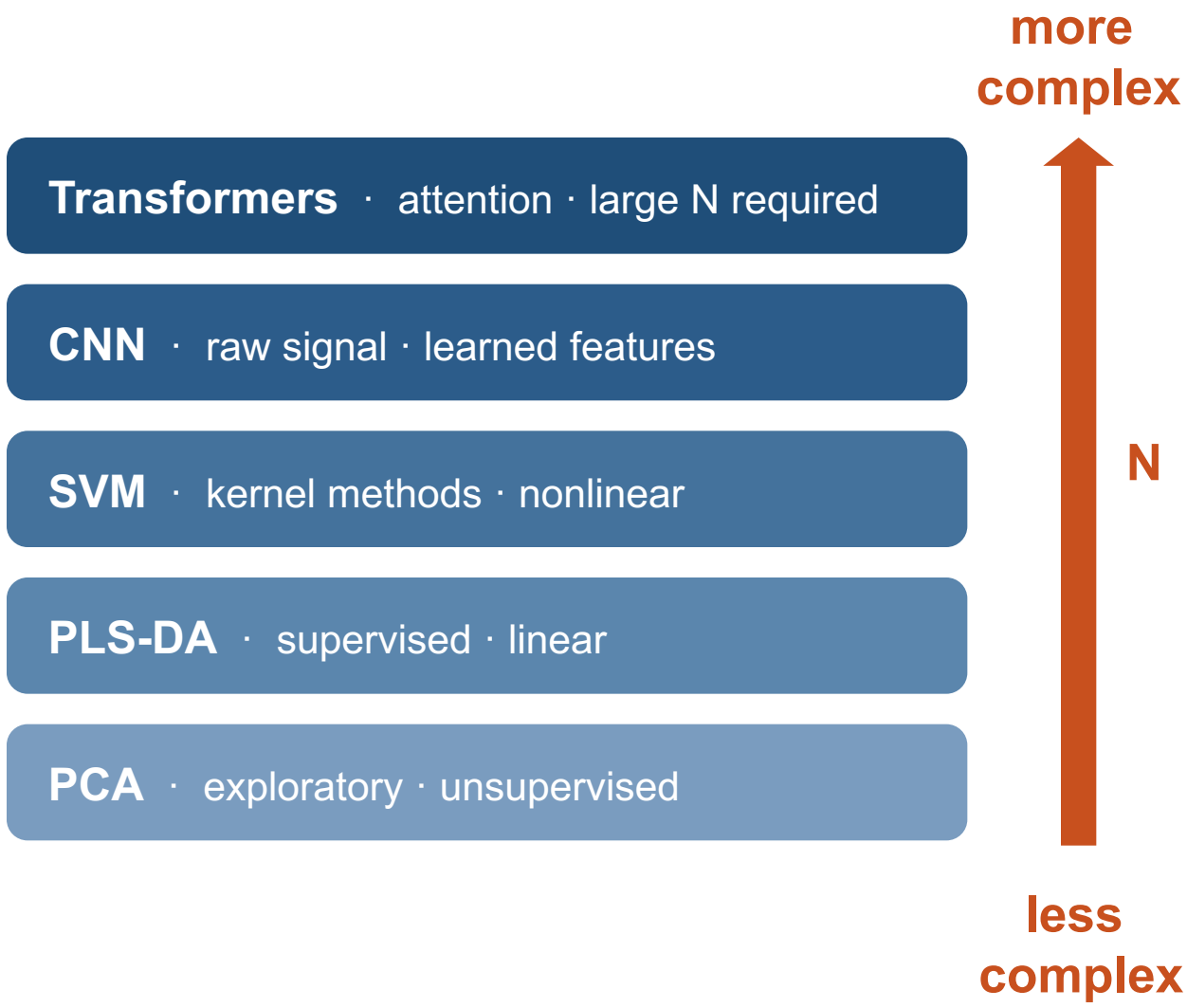
FIGURE · OVERLAPPING VOLTAMMOGRAMS

Overlay: dopamine, serotonin, ascorbic acid, uric acid at physiological pH on a carbon-fiber / BDD microelectrode.
Inset: gas-phase MOS cluster plot



- Multiple analytes often share redox potentials → **peaks overlap**
- The orthogonal-response intuition that works for MOS arrays **does not transfer**
- Selectivity must be earned **at the algorithm layer** — not just by sensor design

Match algorithm to dataset size



ECHEM-ARRAY REALITY

Most published datasets sit at **N = 20–200** samples per class.

Classical methods dominate for a reason.

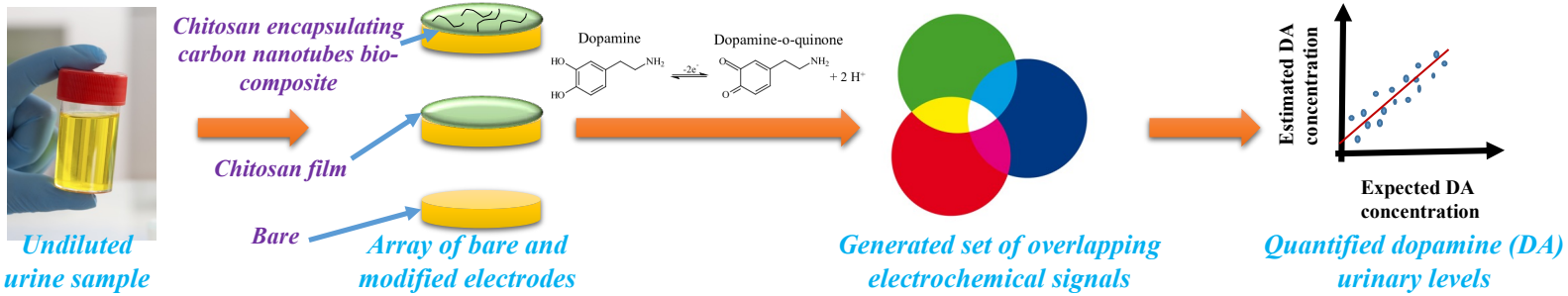
⚠ CAUTIOUS DL NOTE

Deeper architectures don't beat well-engineered **PLS-DA features** unless N is much larger than you probably have.

NBEL case: dopamine vs. norepinephrine

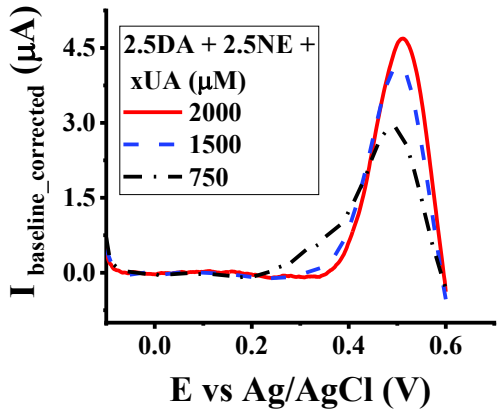
Telling neurotransmitters apart through interferents — what actually worked

PILLAR 1 · NBEL CASE



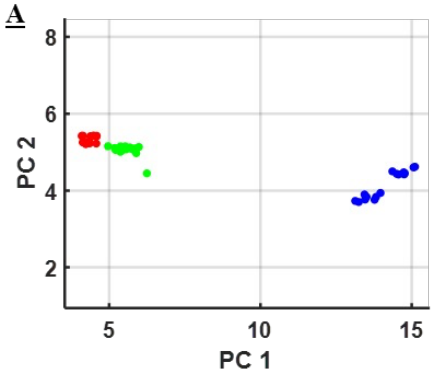
A Overlaid voltammograms

Dopamine, norepinephrine, UA at physiological pH. Peak positions overlap; shape carries the information.



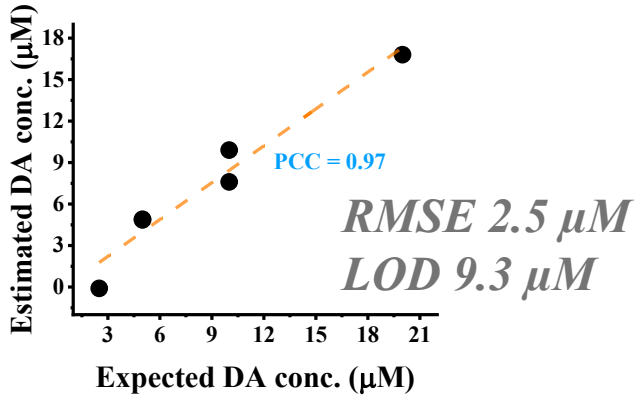
B PCA scores plot

Three classes cluster into separable regions in PC1–PC2 even though voltammogram peaks overlap.



C PLSR prediction

Supervised regression in undiluted urine with a small sample set (6 LVs, 5 features, N=30).



What changed at the algorithm layer: shape features (peak ratio, width, slope, peak heights) — **not deeper architectures.**

OPEN QUESTION

When PCA fails on your data,
is it a *sensor* problem or an *algorithm* problem?

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Pillar 1 takeaway — three principles

1

Match algorithm capacity to dataset size — climb the ladder only when the data justifies it.

2

Engineered voltammogram features (shape, ratio, slope) can beat raw-signal deep learning at the dataset sizes most labs work with.

3

Diagnose unsupervised failures with a supervised method (PLSR) before concluding it's a sensor problem.

★ **KEY READING**

Vlasov, Y., Legin, A., Rudnitskaya, A., Di Natale, C., D'Amico, A. (2005). Nonspecific sensor arrays ("electronic tongue") for chemical analysis of liquids (IUPAC Technical Report). *Pure and Applied Chemistry*, 77(11), 1965–1983.

Why ECHEM calibration is harder

VARIABILITY	**Electrode-to-electrode variability** Even nominally identical electrodes give different baselines — same lithography mask, same batch.
MATRIX	**Matrix effects** Biological fluids modulate response in ways pure aqueous calibration solutions don't capture.
ENVIRONMENT	**Environmental shift** Temperature, pH, ionic strength drift between calibration and use.

→ **Recalibration cost is the dominant operational expense for many deployed ECHEM systems.**

The calibration toolkit — cheap to ambitious

time saved

Learned Representations
autoencoders or other neural feature extractors when interferent structure is unknown

Calibration Transfer
standardize a "slave" sensor or new context to a "master" model when drift sources are enumerable

Multivariate (PLSR)
array-wide regression, more robust to known interferents

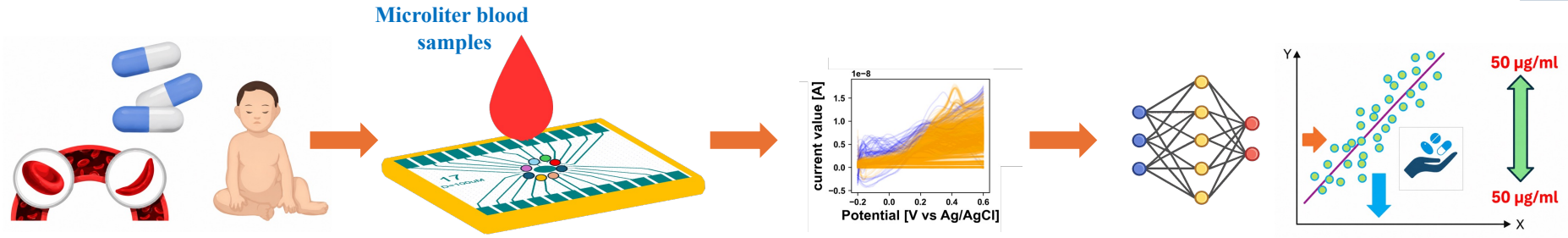
Univariate
single-electrode, single-analyte, frequent recalibration

⚠ **CAUTIOUS DL NOTE**

The right tool depends on what you know about the interference.
For enumerable, approximately-linear drift, calibration transfer is hard to beat.
For unknown interferent structure in complex biofluids, learned representations can find structure your hand-engineered features missed — **always evaluate on held-out data**.

NBEL case: chemometric calibration of a 24-microelectrode array for hydroxyurea in pediatric serum

PILLAR 2 · NBEL CASE



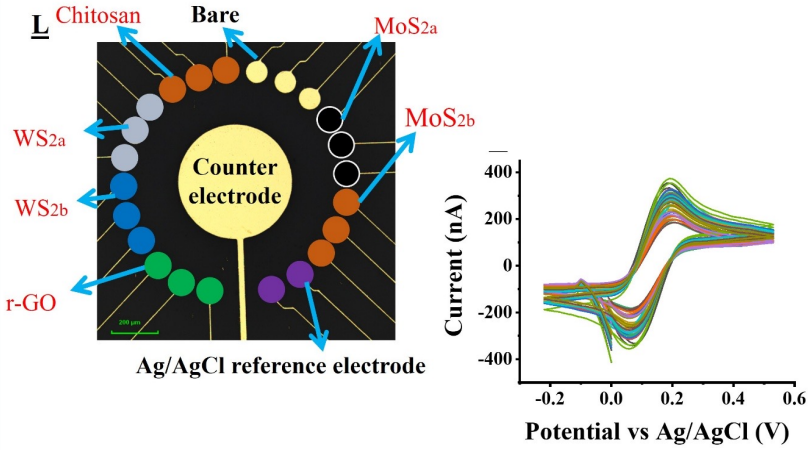
Sickle cell anemia child patient treated with Hydroxyurea

Microelectrode array chip

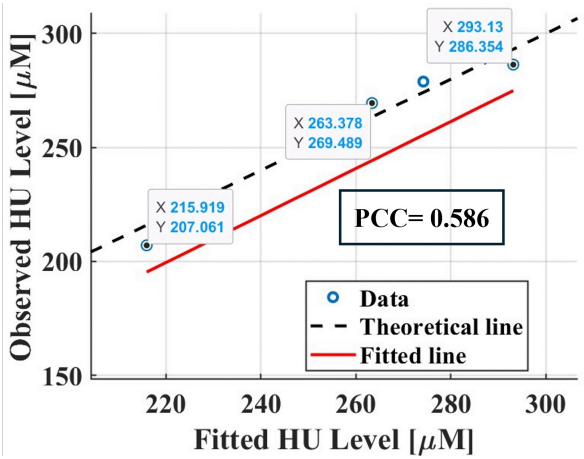
Electrochemical dataset

AI-enabled data analysis for the prediction of Hydroxyurea level

A 24 microelectrodes on a single chip, seven nanomaterial modifications, fabricated together



B 50 children with sickle cell anemia; hydroxyurea measured directly in undiluted serum, no pretreatment



C Three feature extraction strategies tested: engineered peaks, PCA-by-modification, autoencoder

Feature set	Train RMSE	Test RMSE	Test PCC
Autoencoder (HTTH, 13 features)	44.8 µM	**41.9 µM**	0.586
PCA-by-modification (16 features)	43.3 µM	142.1 µM	0.519
Engineered electrochemical peaks (20 features)	43.4 µM	248.7 µM	0.209

All three look equally good on training data (PCCs ~0.94); only the autoencoder generalizes on the held-out test set. Calibration credibility lives in held-out data, not in training fit.

Shukla … Ben-Yoav, Anal. Chem. 2025

QUICK CHECK

How often do you recalibrate your sensors in practice?

- Daily
- Weekly
- Monthly
- Never — calibration drifts unchecked
- Not yet deployed

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Pillar 2 takeaway — three principles

1

Multivariate calibration (PLSR) is the floor — univariate is leaving information on the table.

2

For known drift sources, the e-nose calibration-transfer toolkit is the underused middle rung.

3

For unknown interferent structure in biofluids, learned representations can earn their place — evaluate on held-out data, not training fit.

★ **KEY READING**

Fonollosa, J., Fernández, L., Gutiérrez-Gálvez, A., Huerta, R., Marco, S. (2016). Calibration transfer and drift counteraction in chemical sensor arrays using Direct Standardization. *Sensors and Actuators B*, 236, 1044–1053.

Drift in ECHEM — four superimposed sources

1 Electrode passivation
Slow accumulation on the working surface

2 Reference electrode aging
Ag/AgCl junction potential drifts

compounded — not separable

3 Matrix evolution
the sample itself changes over time

4 Temperature
affects diffusion, kinetics, and reference potential

→ In deployed data, you usually see all four superimposed and can't easily separate them

Three philosophies for handling drift

1 Explicit correction

- Component Correction (CC)
- Orthogonal Signal Correction

✓ **STRENGTH** Simple, transparent, easy to audit

✕ **WEAKNESS** Requires known drift direction

2 Drift modeling

- Recursive PCA
- Kalman filter on baseline

✓ **STRENGTH** Tracks slow drift online

✕ **WEAKNESS** Needs ongoing labeled reference data

3 Domain adaptation

- DANN
- CORAL
- Semi-supervised learning

✓ **STRENGTH** Uses unlabeled data from the drifted state

✕ **WEAKNESS** Assumes covariate, not concept, shift

⚠ **CAUTIOUS DL NOTE**

Domain adaptation is the most powerful tool **and the most dangerous.** It assumes covariate shift (the inputs drift, the input-to-output mapping is stable). When the mapping itself changes (concept drift) domain adaptation makes things worse, **silently.**

Open question

Is drift a bug to correct,
or a signal to read?

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* **The provocative framing is on purpose —** most published work treats drift as noise; the slow component may be a measurement.

Pillar 3 takeaway — three principles

1

Compensate at the aggregate level rather than trying to separate them

Drift in ECHEM has four superimposed sources

2

pair it with a concept-drift detector

Domain adaptation buys the most upside when labeled drift data is unavailable, but assumes covariate shift

3

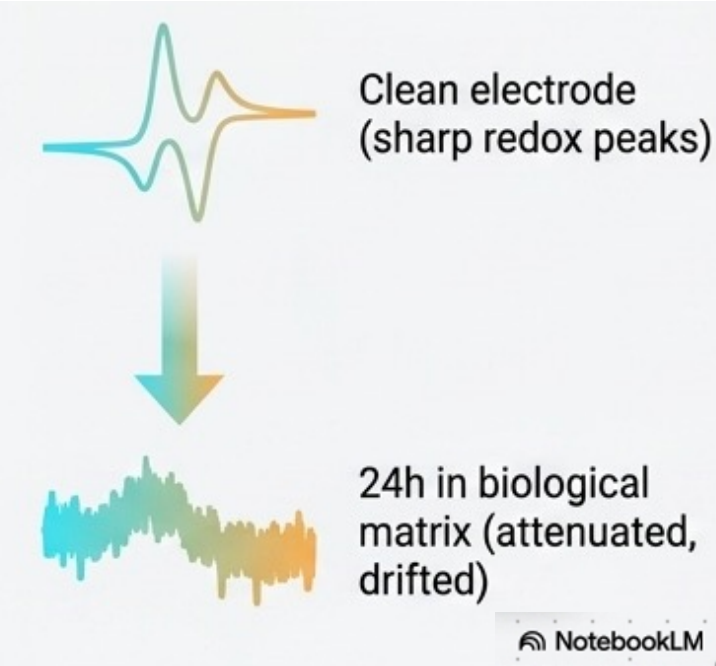
Some drift IS the signal

before you subtract it, ask whether it reports a slow process worth measuring

★ KEY READING

De Vito, S., Fattoruso, G., Pardo, M., Tortorella, F., Di Francia, G. (2012). *Semi-Supervised Learning Techniques in Artificial Olfaction: A Novel Approach to Classification Problems and Drift Counteraction.* IEEE Sensors Journal, 12(11), 3215–3224.

Biofouling — why electrochemical arrays differ



- Proteins, cells, polysaccharides, lipids adsorb on the electrode within minutes of contact with biological media
- Faradaic peaks attenuate; non-faradaic capacitance shifts; signal-to-noise collapses
- Selectivity, calibration AND drift all distort simultaneously — **fouling is upstream of the other three pillars**

This problem is largely unique to ECHEM transduction in biological / aqueous environments

Hurot, C., Scaramozzino, N., Buhot, A., Hou, Y. (2020). Bio-Inspired Strategies for Improving the Selectivity and Sensitivity of Artificial Noses: A Review. Sensors, 20(6), 1803.

Two algorithmic moves: detect, then gate

Don't infer fouling from downstream symptoms — measure it directly

(a) DETECT

Sensor
Voltammetry + EIS

→ **Impedance features extraction**
R_s, R_ct, C_dl, Warburg

→ **Anomaly model**
1-class SVM · autoencoder · statistical control

→ **Fouling state estimate**
clean / fouled + probability

(b) COMPENSATE / GATE

Adjust inference
Feed fouling features as covariates → correction

Reject sample (gate)
If P(foul) > threshold, suppress the analyte readout

Trigger renewal
Electrochemical cleaning, flush, or replacement

⚠ **CAUTIOUS DL NOTE**
almost no public benchmark datasets for fouling-aware ECHEM learning. Classical equivalent-circuit features and one-class anomaly detectors still outperform end-to-end DL at the dataset sizes most labs collect.

Scherer, B., et al., (2021). Digital electrical impedance analysis for single bacterium sensing and antimicrobial susceptibility testing. Lab on Chip, 21(6), 1073.

Quick check · your setup

Can your platform tell, in real time, when it's been biofouled?

A. Yes — explicit fouling channel

B. Partial — I infer from drift / recalibration failure

C. No — I find out offline or after the fact

D. Not yet deployed in a fouling-prone environment

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Pillar 4 takeaway — three principles

1

Detect fouling explicitly

It's upstream of selectivity, calibration, and drift. Don't infer it from downstream symptoms — by then your analyte signal is gone.

2

Fuse modalities for transparency

EIS + voltammetry (+ offline optical) lets you gate analytical inference on a visible fouling state.

3

The data gap IS the bottleneck

Public fouling-aware benchmark datasets are the most valuable contribution

★ ALGORITHMIC SIDE

Scherer, B., Surrette, C., ... Potyrailo, R.A., ... Puleo, C.M. (2021). Digital electrical impedance analysis for single bacterium sensing and AST. Lab on a Chip, 21(6), 1073–1083.

★ MATERIALS / FRAMING

del Valle, M. (2016). Bioelectronic Tongues Employing Electrochemical Biosensors. In: Trends in Bioelectroanalysis, Vol. 6, Springer.

Five common failure modes — and their diagnoses

1. Overfitting at small N

200-parameter MLP on 50 samples → 99% train, 60% test.
Dx: Climb DOWN the ladder. Try PLSR first.

2. PDS with no shared mechanism

Donor and recipient sensors don't share redox chemistry.
Dx: PDS assumes linear mapping — check chemistry before applying.

3. Drift correction erases the signal

Over-aggressive Component Correction strips the analyte direction.
Dx: Validate against a known concentration time course.

4. DL on unbalanced classes

Accuracy 99%; minority recall catastrophic.
Dx: Report balanced accuracy, AUC — not raw accuracy.

5. Validation leakage

Splitting by sample instead of by sensor / day.
Dx: Stratify by the deployment variable you must generalize across.

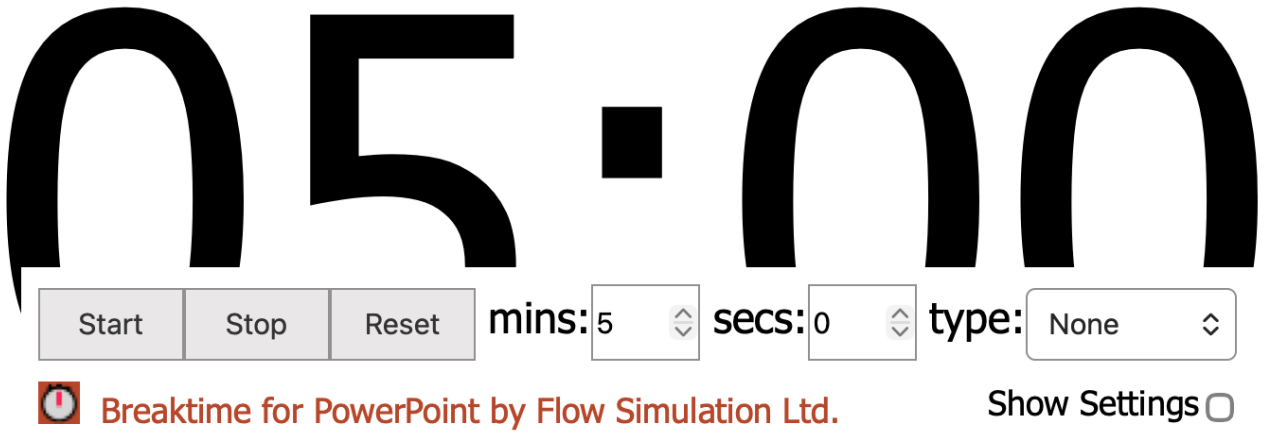
Most surprising performance failures in published ECHEM-ML come from these five.
Watch for them in your own work.

Try it yourself (~5 minutes)

GitHub

- Load the page on your laptop.
  - https://nbelbenyoav.github.io/Isoen2026-HandsOn/

- Steps:
  - (1) Look at the data →
  - (2) PCA on raw signal →
  - (3) Toggle features →
  - (4) Train a small MLP



Debrief

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The cautious-DL summary

"Most ECHEM-array problems are solved by better features and honest validation, not deeper networks."

WHEN TO CLIMB THE DL LADDER

- ✓ Donor dataset much larger than recipient — transfer learning earns its place
- ✓ Genuinely nonlinear mismatch between sensors or environments — domain adaptation helps
- ✗ Hoping a transformer fixes poor sensor design — no, it won't
- ✗ Dataset under a few hundred samples per class — classical methods beat DL here

Where algorithmic effort can contribute

	KNOWN target / conditions	UNKNOWN or shifting
SENSOR LEVEL	**Hardware fundamentals** • Electrode geometry & surface chemistry • Material selection for the target redox couple • Calibration in clean buffer	• Antifouling coatings • Redundant electrodes • Reference channels
ALGORITHM LEVEL	**Pillar 1: PCA / PLS-DA / PLS regression** • Engineered voltammogram features • Honest validation by sensor / day	**Pillars 2-4: where the toolkit lives** • Calibration transfer • Drift correction + domain adaptation • Multimodal fouling detection

Cross-pollination — who borrows what

E-nose → ECHEM

- Calibration transfer methodology (PDS, deep transfer)
- Ensemble classifier traditions for drift
- Public benchmark dataset culture

ECHEM → E-nose

- Redox-aware feature engineering
- Impedance-based fouling diagnostics (humid / biofilm)
- In vivo and in-fluid deployment lessons

Both communities are at this conference. The exchange should happen at the coffee breaks. Use them.

Final question · word cloud

If you started a new ECHEM-array project tomorrow, which pillar would you tackle first?

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Thank you. Hadar Ben-Yoav · benyoav@bgu.ac.il · Nanobioelectronics Lab — Ben-Gurion University of the Negev
Sitting on long-duration ECHEM data with drift or fouling phases? Let's talk about open benchmarks.