Hidden Dynamical Structure in Stochastic Intracellular Calcium Dynamics

Shakul Awasthi[1]
in collaboration with Jaesung Choi[2], Athokpam Langlen Chanu[3,4]

[1]School of Physics, KIAS, Seoul [2]Center for AI and Natural Sciences, KIAS, Seoul
[3]Department of Physics, POSTECH, Pohang [4]APCTP, Pohang

Nonequilibrium Statistical Physics of Complex Systems 2026

Calcium: a universal cellular messenger with a temporal code

- Cytosolic Ca^{2+} oscillations carry a **temporal code** tied to physiological states in health and disease.
- Deterministic models of Ca^{2+} dynamics predict distinct dynamical regimes:
  - steady state, oscillatory, bursting,
  - chaotic, multiple periodicity (period-2/3/4), quasiperiodic.
- But real cells are **intrinsically stochastic**: finite molecule numbers make these regimes blur together.

Central question

Do the organizational structures predicted by deterministic theory remain **detectable** under biologically realistic noise?

Houart's model: the deterministic backbone

Three coupled concentrations, cytosolic Ca^{2+} (x), stored Ca^{2+} (y), and InsP_3 (z):

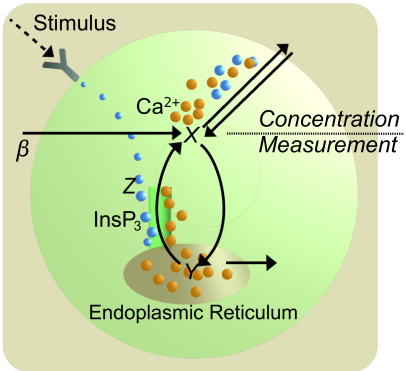
Deterministic dynamics (Houart *et al.*, 1999)

$$\dot{x} = V_0 + V_1\beta - V_2 + V_3 + k_f y - kx$$
$$\dot{y} = V_2 - V_3 - k_f y$$
$$\dot{z} = \beta V_4 - V_5 - \varepsilon z$$

Saturable, Hill-type fluxes:

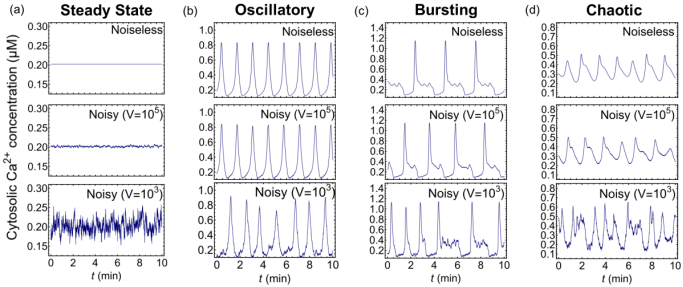
$$V_2 = V_{M2}\frac{x^2}{K_2^2+x^2}, \quad V_5 = V_{M5}\frac{x^n}{K_d^n+x^n}\frac{z^p}{K_5^p+z^p},$$
$$V_3 = V_{M3}\frac{x^m}{K_x^m+x^m}\frac{y^2}{K_y^2+y^2}\frac{z^4}{K_z^4+z^4}.$$

CICR (V_3): Ca^{2+} activates its own release (positive feedback), coupled to **Ca^{2+}-activated InsP_3 degradation** (V_5, negative feedback).



CICR / InsP_3 feedback schematic

Noise erases the visual signatures

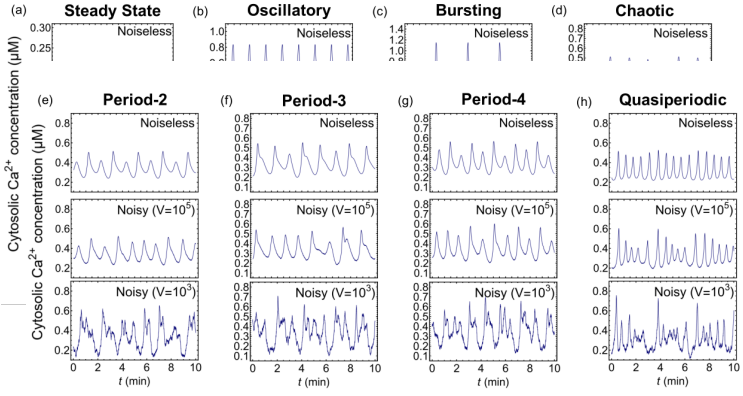


Top row (noiseless): states clearly separable.

Bottom row ($V = 10^3$): **chaos and multiple periodicity become visually ambiguous.**

Classical statistical measures (e.g. permutation entropy) struggle exactly here, so we turn to a learned classifier.

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Stochastic model: chemical Langevin dynamics

- Nonlinear Houart Ca^{2+} model, driven by Ca^{2+}-**induced** Ca^{2+} **release** (CICR).
- Intrinsic fluctuations from finite molecule counts via the **Chemical Langevin Equation (CLE)**.

Noise set by system size V

$$\dot{\boldsymbol{s}} = \underbrace{\boldsymbol{f}(x,y,z)}_{\text{deterministic}} + \frac{1}{\sqrt{V}}\underbrace{\boldsymbol{G}(x,y,z)\,\boldsymbol{\xi}(t)}_{\text{intrinsic noise}}$$

Fluctuation amplitude $\sim 1/\sqrt{V}$; $V \to \infty$ recovers the deterministic limit.

- $x(t)$: cytosolic Ca^{2+} concentration (the observable).
- Physiological range 0.1–1 μM; periods sec$-\sim$30 min.
- A single parameter V tunes correlated noise across the whole reaction network.

From reaction channels to the chemical Langevin equation

- The ODE model is reformulated as **elementary reaction channels** on the populations X, Y, Z.
- Each channel R_j carries a **state change** and a **propensity** a_j. In Gillespie's formalism, $a_j\,dt$ is the probability that R_j fires during $(t, t+dt)$.

Reaction channels (12 in total)

Process	Channel	a_j
Stimulated Ca^{2+} entry	$X \to X+1$	$VV_1\beta$
CICR release	$X \to X+1$	VV_3
Ca^{2+} efflux	$X \to X-1$	Vkx
Pumping to store	$Y \to Y+1$	VV_2
$InsP_3$ synthesis	$Z \to Z+1$	$V\beta V_4$
$InsP_3$ degradation	$Z \to Z-1$	VV_5
⋮		

. . . 12 channels in total for X, Y, Z (birth and death processes).

Approximating each channel's firing count as Gaussian gives the **CLE**:

$$\frac{d\boldsymbol{s}}{dt} = \boldsymbol{F}(x,y,z) + \frac{1}{\sqrt{V}}\,\boldsymbol{G}(x,y,z)\boldsymbol{\xi}(t).$$

- One **independent** ξ_j per channel ($M = 12$). giving fluctuation–response consistency.
- Channels affecting multiple species generate **correlated** fluctuations.
- Noise $\sim V^{-1/2}$; Deterministic as $V \to \infty$.

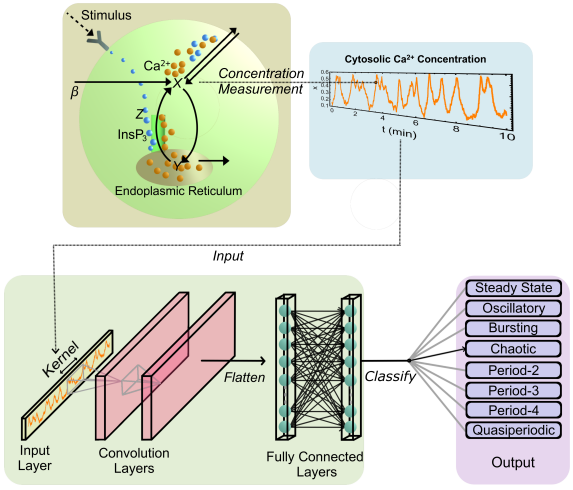
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Chemical Langevin equations

$$\begin{bmatrix}\dot{x}\\ \dot{y}\\ \dot{z}\end{bmatrix} = \begin{bmatrix}V_0 + V_1\beta - V_2 + V_3 + k_f y - kx\\ V_2 - V_3 - k_f y\\ \beta V_4 - V_5 - \varepsilon z\end{bmatrix} + \frac{1}{\sqrt{V}}\begin{bmatrix}\sqrt{V_0}\,\xi_1 + \sqrt{V_1\beta}\,\xi_2 - \sqrt{V_2}\,\xi_3 + \sqrt{V_3}\,\xi_4 + \sqrt{k_f y}\,\xi_5 - \sqrt{kx}\,\xi_6\\ \sqrt{V_2}\,\xi_7 - \sqrt{V_3}\,\xi_8 - \sqrt{k_f y}\,\xi_9\\ \sqrt{\beta V_4}\,\xi_{10} - \sqrt{V_5}\,\xi_{11} - \sqrt{\varepsilon z}\,\xi_{12}\end{bmatrix}$$

Workflow: simulate, train, classify, deploy



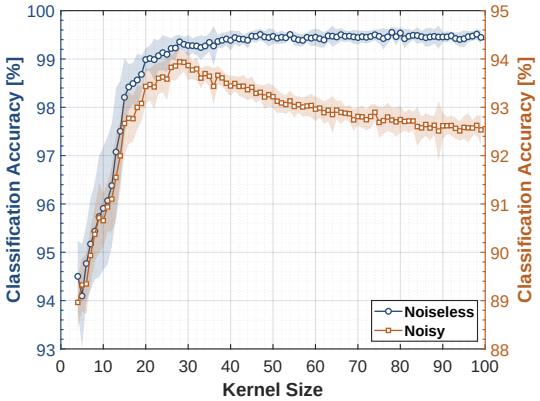
Labels come from simulation for training; the trained network is then applied to **real experimental traces**.

Why *large* kernels, and how large?

- Small-kernel CNNs miss **long-range temporal structure**; bursting and P-3/P-4 span many cycles.
- **Large-Kernel CNN (LKCNN)**: wide temporal receptive field captures global dynamical structure.
- Trade-off: too large a kernel blurs short-scale detail.

Optimal kernel

Noiseless: accuracy *saturates* with large k.
Noisy: accuracy **peaks at moderate** k, so $k = 28$ is used throughout.

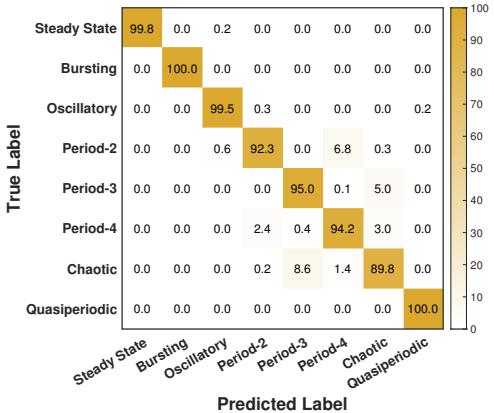


Accuracy vs. kernel size: noiseless (top) vs. noisy (bottom).

High accuracy on synthetic data, even under noise

- $>$**90%** accuracy across all eight states at realistic noise levels.
- Most states identified with near-perfect reliability.
- Residual confusion is **physically meaningful**: between *chaos* and *multiple periodicity*, states that overlap in temporal signature.

e.g. under noise, 8.6% of chaotic traces read as P-3; P-2 occasionally read as P-4.

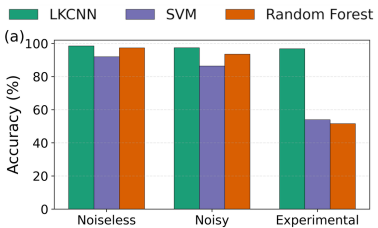


Confusion matrix, realistic-noise test set.

Generalization to real cells, and it beats the baselines

- Experimental Ca^{2+}: pancreatic β-cells, WT-HEK293, STIM-KO, ORAI TKO.
- Curated 3-class benchmark vs. human annotation.
- LKCNN: **96.8%** on experimental traces.
- FFT-based baselines collapse on real data: **SVM 54.0%**, **RF 51.6%**.

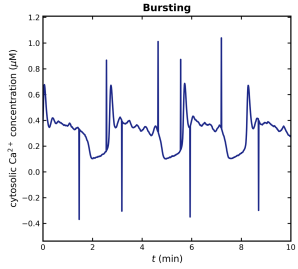
LKCNN keeps a small synthetic-to-experiment gap; the baselines do not.

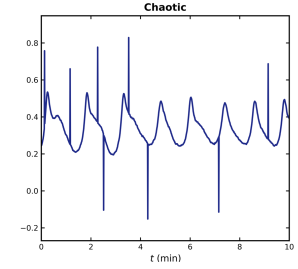


Accuracy across conditions.

Robust to spike-like corruption

- Fluorescence imaging adds sparse, large-amplitude **impulsive spikes**.
- Accuracy *drop* under corruption:
  - LKCNN: only **2.6% / 3.5%**
  - RF: 12.8%/15.4%
  - SVM: 44.1%/49.3%
- **Why?** The large receptive field integrates over long windows, so isolated spikes barely move the learned representation.
- FFT features are *global*: one bad point distorts the whole spectrum.





Conclusions & outlook

- A deep-learning framework classifies **eight** Ca^{2+} dynamical states from raw time series, with **no manual feature engineering**.
- An optimized **LKCNN ($k = 28$)** is robust across a broad range of intrinsic noise.
- $> 90\%$ on noisy synthetic data; **96.8%** on experiment, far above SVM (54.0%) and RF (51.6%).
- Deterministic dynamical signatures **remain detectable** under realistic stochasticity.

Outlook

Beyond classification: **simulation-based inference** to recover hidden physiological parameters directly from noisy fluorescence traces.

Thank you

Questions & discussion welcome!

References

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What the states mean, and why this works

Biological reading of the regimes:

- steady state: resting cell
- simple oscillations: signaling / homeostasis
- bursting: linked to apoptosis
- multiple & quasi-periodicity: phenotype-specific behavior
- chaos: an open question in biological dynamics

Why LKCNN succeeds:

- Learns **global dynamical structure**, not isolated peaks.
- Robust to noise, heterogeneity, and short records.
- Bridges **deterministic theory** and **stochastic biological reality**.

Take-home physics

The parameter-dependent dynamical organization of a nonequilibrium reaction network is **preserved and computationally detectable** through realistic intrinsic noise.