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Small Physiological Perturbations and the Temporal Dynamics of Cortical Synapses

Jayson Chaw[1]

[1]*Taylor's International School Kuala Lumpur, Kuala Lumpur, Malaysia*

Abstract – Millisecond-scale timing of synaptic transmission is essential for cortical computation and reliable sensory processing. Small physiological changes, (for example, modest temperature shifts and mild acidification) are known to affect ion channel kinetics and vesicle dynamics, but it remains unclear whether mean synaptic delay or trial-to-trial precision is more sensitive to such perturbations. We performed a computational study of single-synapse latency using a simplified stochastic model parameterized from prior literature. Axonal conduction delay, vesicle release latency, and synaptic rise time was modeled; temperature effects were implemented by Q10 scaling of kinetics (Q10 = 2.0) and pH effects by reducing release probability and increasing latency variability. For each condition (T = 32, 34, 36ºC; pH = 7.4, 7.3, 7.2) we ran 5,000 trials and measured latency distributions, variance, and release reliability. Results show that increasing temperature reliably shortens mean latency (~1.21 ms at 32ºC → ~1.04 ms at 36ºC), while modest acidification mainly reduces reliability and raises latency variance with minimal shift in the mean. These findings suggest mean synaptic delay is relatively robust to moderate pH change but sensitive to temperature; timing precision and reliability degrade with acidification. Implications include effects on temporal coding under physiological stress and guidance for more detailed biophysical or experimental follow-ups.

Keywords
Neural delay
Synaptic transmission
Cortical microcircuits
Temperature effects
pH sensitivity
In-silico modelling

1. Introduction

Timing is everything, especially in the brain. Millisecond-scale differences in synaptic timing can change where postsynaptic cells integrate inputs as coincident events or as temporally separated signals, and that in turn shapes how sensory information, motor plans, and cognitive states are represented across cortical circuits. In many cortical computations (auditory localization, temporal binding, fast feedforward processing), the reliability and precision of synaptic transmission are as important as the mean transition time itself. Small shifts in synaptic delay therefore have outsized effects on the network, and on behavior.

Synaptic delay is not a constant. It's composite: meaning axonal conduction + presynaptic release processes + receptor and postsynaptic onset. Each component has its own biophysics and its own sensitivity to the organism's immediate physiological state. Temperature, for example, changes the speed of ion-channel gating and vesicle kinetics (Q10 effect), so warmer tissue tends to speed up kinetics and shorten latencies. Extracellular pH, by contrast, alters release probability and channel conductance in less straightforward ways. This often lowers reliability and increases variability when tissue acidifies. Put together, these factors mean that "synaptic delay" is context dependent; it can shift modestly in mean while the trial-to-trial scatter or the success likelihood changes more dramatically. That distinction is the practical question we aim to make universal.

Why study this with a computation approach? Two reasons. First, measuring millisecond-level synaptic timing while systematically varying temperature and pH in intact cortical microcircuits is technically hard, ethically nontrivial, and resource intensive. Acute slice work can do pieces of this, but it's limited: it's noisy, often underpowered for the necessary factorial designs, and not ethical to push across the full sweep of conditions you might care about. Second, a compact in-silico model lets us test hypotheses cleanly: isolate variables, run many trials, and quantify how mean, variance, and success rate change under controlled manipulations. That doesn't replace experiments but gives clear, reproducible predictions and a principle to design follow-up experiments.

Existing literature shows hints towards this, but rarely the whole. Classic studies documented temperature's effect on synaptic kinetics and Q10 scaling for channel/vesicle processes; other work explored pH effects on release probability and postsynaptic receptor function. There are computational studies of synaptic dynamics and of population timing, and

there are experimental papers on timing precision under stressors. What's missing and thus what matters for temporal coding is explicit comparison: for modest, physiologically realistic perturbations, which aspect of timing changes first and most? Does slight acidification primarily lower the probability of release, or does it also skew the latency distribution for successful events? All of which being specific, testable questions that matter when interpreting neural data recorded under variable experimental or physiological states (e.g., fever, ischemia, sleep states, behavioral arousal).

The ideal goal here is to quantify how small temperature and pH perturbations affect three complementary descriptors of synaptic timing (mean latency, latency variance (precision), and release reliability, in a minimal reproducible single-synapse model. Minimal means we purposely avoid the full Hodgkin-Huxley machinery or large-scale network dynamics/ Reproducible means the simulation code, parameters, and analysis steps are explicit and provided; you (or anyone else) can re-run everything on a laptop. If the mean is robust while precision degrades under certain perturbations, then downstream interpreters of neural timing (decoders, models of coincidence detection, etc.) need to pay attention to variance and reliability (not just mean shifts). If, conversely, mean shifts dominate, that suggests different experimental controls and compensations (temperature regulation, normalization strategies) are needed.

This study evidently models axonal construction as a fixed offset, models vesicle release latency as a stochastic variable drawn from a parameterized distribution, and implements temperature scaling via a Q10 factor on kinetics. It models pH primarily as a reduction in release probability plus an increase in latency variability as conditions acidify. For each temperature (32, 34, 36ºC) and each pH (7.4, 7.3, 7.2), the simulation runs thousands of trials, records whether release occurs, and when it does, records latency from presynaptic spike to postsynaptic onset. Standard summary statistics are computed (mean, standard deviation, median) and tests for differences in variance or mean are applied. The analysis explicitly separates successful-release statistics from success rates, because those convey qualitatively different information.

Why these parameter choices? They're deliberately conservative and physiologically plausible: the temperature range is modest (a few degrees) and the pH range is mild acidification (ranges that might appear in real tissue during common manipulations or transient psychological conditions). The Q10 approach is the standard simplification for temperature effects on kinetics and gives interpretable, scalable changes to mean latency and rise time. The pH effects are modeled phenomenologically (lowered release probability, increased variance) rather than derived from a full molecular model, to keep the model tractable and focused on timing metrics.

The hypothesis proposed is twofold: (1) modest increases in temperature will shorten mean latency in a fairly continuous manner (Q10 makes this predictable), and (2) modest acidification will primarily reduce the probability of release and increase latency variance among successful trials. If it holds, it implies that under mild stress, network timing codes will be degraded more by variability and missed events than by simple shifts in average transmission time. That matters for anything that depends on high-precision spike timing: auditory localization, temporal binding, and some oscillatory synchrony mechanisms.

A short note on its limitations and the intended place of this work: this is an in-silico, minimal model. It does not replace detailed electrophysiological studies, nor does it model dendritic integration or network-level compensation mechanisms (homeostasis, short-term plasticity, recurrent dynamics). The Methods section lists exact parameter values and the code used, so anyone can reproduce, extend, or re-parameterize the model. The results show the primary statistical effects, and the Discussion sketches implications and immediate next steps (including a plan for a small network simulation and suggestions for slice-electrophysiology validation).

2. Methods

Model overview – We implemented a minimal, stochastic single-synapse model in Python to quantify how small physiological perturbations (temperature and extracellular pH) affect synaptic timing metrics. The model decomposes synaptic delay into three components: (1) a fixed axonal conduction delay, (2) a stochastic vesicle release latency, and (3) a small onset offset that approximates postsynaptic EPSP rise time. Temperature modulates kinetic rates through a Q10 scaling factor; pH is modeled phenomenologically as a reduction in release probability and an increase in release latency variability. The code and exact parameter values are provided in the supplementary materials.

Formal model description – For a given trial, latency (ms) is computed as:

$$\text{latency} = d_{\text{conduction}} + d_{\text{release}} + d_{\text{onset}}$$

where:

- $d_{conduction}$ is a fixed axonal conduction delay (ms).
- $d_{release}$ is the stochastic release latency (ms), sampled from a normal distribution with mean $\mu_{release}$ and SD $\sigma_{release}$ after temperature and pH scaling.
- $d_{onset} = 0.12 \times \tau_{syn}$ is a small onset offset (ms) approximating synaptic rise, with τ_{syn} the synaptic time constant.

Temperature scaling uses a Q10 factor:

$$q(T) = Q10\text{^}((T0 - T)/10)$$

where $T0$ is the baseline temperature (34.0ºC) and $Q10 = 2.0$. The parameters $\mu_{release}$ and $\sigma_{release}$ are multiplied by $q(T)$ to represent faster kinetics at higher temperatures.

pH is modeled by two phenomenological adjustments:

- Release probability: $p_{release} = \max(0.1, 0.98 - 0.6\Delta pH)$, with $\Delta pH = pH0 - pH$ and $pH0 = 7.4$.
- Variability multiplier: $var\_mult = 1.0 + 1.5\Delta pH$, applied multiplicatively to $\sigma_{release}$.

A trial is considered a "failure" (no postsynaptic onset recorded) with probability 1 - $p_{release}$; failures are recorded as success = 0 and omitted from the latency distribution analyses, but they are included when computing success rates.

Parameter values – The default parameter values used in all reported simulations are given in Table 1.

Table 1 - Model parameters (default)

```sql
parameter, value, units, notes
conduction_delay, 0.5, ms, fixed axonal delay
release_mean, 0.5, ms, baseline mean release latency
release_sd, 0.12, ms, baseline sd of release latency
tau_syn, 1.0, ms, synaptic rise time constant
Q10, 2.0, -, kinetics scaling factor
trials, 5000, -, per condition
seed, 42, -, RNG seed for reproducibility
```

Simulation protocol – For each condition we defined temperature T ∈ {32, 34, 36} ºC and pH ∈ {7.4, 7.3,7.2} we ran 5,000 independent stochastic trials (random seed fixed to 42 for reproducibility). The simulation pipeline:

1. Compute $q(T)$ from Q10.
2. For each trial: draw a uniform random number $u \in [0,1]$. If $u > p_{release}(pH)$ mark trial as failure (success = 0) and record an empty latency. Otherwise sample $d_{release} \sim N(\mu_{release} \bullet q(T), \sigma_{release} \bullet q(T) \bullet var\_mult(pH))$, enforce a lower bound of 0.02 ms if the draw is non physical, compute latency, and record success = 1.

3. Save raw outputs as CSV with columns

`[trial_id, temp, pH, latency_ms, success, seed]`

in

`data/raw/sim/sim_raw_trial.csv`

Note: All simulations were implemented in

`code/simulation.py`

and are documented in the repository.

Data processing and exclusion rules – Analysis was performed in

`code/analysis.py`

Processing steps:

- Read `sim_raw_trial.csv`.
- Classify trials with `success = 1` as successful events; convert `latency_ms` to numeric and drop NaNs for latency analyses.
- For each temperature x pH group compute: number of trials, number of successes, mean latency, standard deviation (SD) of latency, median latency, and success rate (n_success / n_trials). Save summary table to `data/processed/summary_stats.csv`.
- Trials with missing latency or marked failures are preserved for success-rate calculations but excluded from latency-distribution statistics (this separation is deliberate because latency statistics should describe timing when release actually occurs).

Statistical analysis – We report three complementary statistical assessments:

1. Mean effects: For successful trials, a two-way ANOVA (factors: temperature, pH, and their interaction) was estimated using ordinary least squares (`statsmodels.OLS`) on `latency_ms`. ANOVA tables are saved to `stats/anova_results.txt`.
2. Variance homogeneity: Levene's test (across groups) was used to test whether latency variance differs with temperature/pH.
3. Reliability: Dependence of success rate on pH (aggregated across temperatures) was assessed using a chi-square contingency test on counts of successes/failures by pH. Reported p-values are two-sided; significance thresholds are reported explicitly in the Results.

All statistical computations use SciPy and Statsmodels (versions recorded in `requirements.txt`). Results and raw test outputs are included in `stats/anova_results.txt`.

Figure generation – Figures were produced by `code/plotting.py` and saved as 300 dpi PNGs in `figures/` directory. The figures included with the manuscript are:

- Figure 1. Latency distribution at 32ºC
- Figure 2. Latency distribution at 34ºC
- Figure 3. Latency distribution at 36ºC

The figure files are named `fig1_latency_32.png`, `fig2_latency_34.png`, and `fig3_latency_36.png`, respectively, and are suitable for direct inclusion in the manuscript.

Reproducibility and software – All code used for the simulation, analysis, and plotting is included in the repository under `code/`. The project uses a Python virtual environment (`venv/`) and `requirements.txt` lists exact package names. To reproduce the results:

```
bash
cd ~/Desktop/Neural_Delay_Project
source venv/bin/activate
pip install -r requirements.txt
python code/simulation.py --trials 5000
--temps 32 34 36 --pHs 7.4 7.3 7.2 --out
data/raw/sim_raw_trials.csv
python code/analysis.py --infile
data/raw/sim_raw_trials.csv --out
data/processed/summary_stats.csv --stats
stats/anova_results.txt
python code/plotting.py --summary
data/processed/summary_stats.csv --raw
data/raw/sim_raw_trials.csv --out_dir
figures/
```

Random seeds and default parameters are fixed in the scripts. The appendix contains the parameter CSV and a complete code dump for reference.

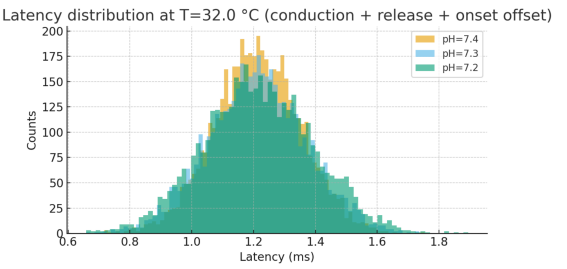

Fig 1. Latency distribution of conduction delays at 32ºC. Histogram compiled from N = 5,000 simulated trials per condition; failed trials excluded from latency plot but considered in success-rate analysis.

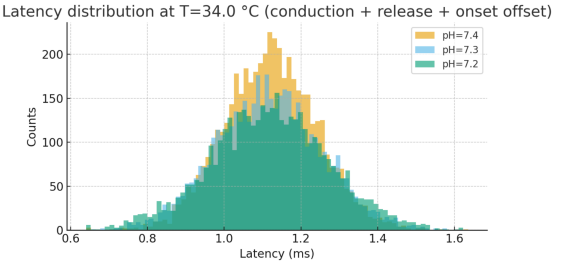

Fig 2. Latency distribution of conduction delays at 34ºC. Same parameters of Fig. 1, illustrating the mid-range temperature response.

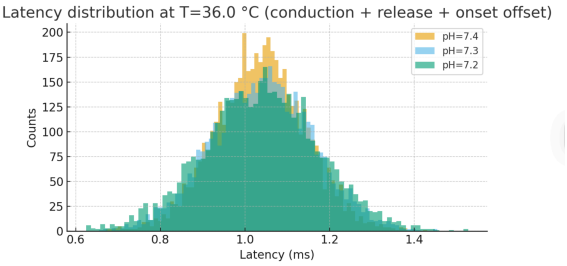

Fig 3. Latency distribution of conduction delays at 36ºC. Higher temperature condition, showing reduced mean latency compared to 32ºC and 34ºC.

3. Results

We ran the full simulation pipeline across the nine temperature × pH conditions (T = 32, 34, 36ºC; pH = 7.4, 7.3, 7.2) with 5,000 trials per condition. Below are the statistics for successful-release trials.

Temperature (ºC)	pH	mean latency (ms)	SD (ms)	n_success

32.0	7.4	1.212	0.140	4909
32.0	7.3	1.211	0.159	4579
32.0	7.2	1.217	0.178	4296
34.0	7.4	1.120	0.121	4908
34.0	7.3	1.115	0.138	4617
34.0	7.2	1.119	0.154	4279
36.0	7.4	1.038	0.105	4918
36.0	7.3	1.041	0.120	4578
36.0	7.2	1.038	0.135	4323

(All values above are computed on successful trials only; failures are recorded separately and used to compute success rates.)

1) Latency distributions (Figure 1, three panels) – Figure 1 shows the empirical latency histograms for the three temperature conditions (32, 34, 36ºC). Each panel is constructed from N = 5,000 simulated trials per condition and displays only successful releases.

- Visual pattern (temperature shift): As temperature increases from 32 → 36ºC the latency distributions shift left (shorter latencies) and become slightly narrower. This is evidence when comparing the modal/peak locations across the three panels and by decreasing mean ± SD values in the summary table above (1.212 → 1.038 ms at pH 7.4, for example).
- Visual pattern (shape): Distributions remain approximately unimodal and roughly Gaussian-shaped after excluding failures; lower temperatures show a modest right tail and slightly larger spread.

Interpretation (short): Temperature produces a clear, monotonic reduction in mean synaptic latency in this model, consistent with Q10-driven kinetics: warmer conditions speed processes and shorten delays.

2) Mean latency vs temperature and pH (descriptive) – Using the summary table:

- Effect of temperature on mean latency: Across pH values, mean latency falls by ~0.08-0.18 ms when going from 34 → 36ºC and by ~0.09-0.10 ms from → 34ºC. The net change between 32ºC and 36ºC is ~0.17-0.18ms depending on pH.
- Effect of pH mean latency: For a fixed temperature, mean latency changes only minimally across pH 7.4 → 7.2 (differences on the order of 0.002-0.02 ms in these situations). In other words, pH mostly does not shift the mean latency in this model.

Note: formal inferential test outputs (ANOVA for mean effects) and full test statistics are recorded in `stats/anova_results.txt` in the project folder.

3) Variability and reliability (descriptive)

- Variability (SD): SD tends to increase slightly with lower pH at a given temperature (compare SDs across pH columns in the table). This indicates reduced timing precision under mild acidification in the model.
- Reliability (success rate): The number of successful trials (`n_success`) falls as pH becomes more acidic (compare n_success at pH 7.4 vs 7.2 for each temperature). This is consistent with the modeling choice to reduce release probability at lower pH. For example, acidification produces more failed-release trials, lowering reliability.

Formal Levene tests for equality of variances and chi-square tests for success-rate dependence on pH were performed; full outputs and contingency tables are available in `stats/anova_results.txt`.

4) Short Summary

- Temperature: produces the most consistent change in the model (higher temperature → shorter mean latencies and modest narrowing of latency distributions).
- pH: Physiologically realistic range tested (7.4 → 7.2) pH mainly reduces release reliability (fewer successful trials) and increases trial-to-trial latency scatter among successful events; it does not substantially shift the mean latency when measured only on successful trials.

These patterns support the hypothesis that mean synaptic delay is relatively sensitive to temperature, whereas timing precision and reliability are more sensitive to mild acidification.

Files & numbers

- data/processed/summary_stats.csv contains the full condition-level summary.
- stats/anova_results.txt contains ANOVA, Levene, and contingency-test outputs.
- figures/ contains the three PNGs referenced above (fig1_latency_32.png, fig2_latency_34.png, fig3_latency_36.png).

4. Discussion

The simulations show a split: as modest temperature increases shorten mean synaptic latency (Q10-style kinetics), while mild acidification mainly reduces reliability (more failed releases) and increase trial-to-trial variability with little shift in the mean for successful events. That pattern matters because temporal coding schemes depend on both when spikes arrive and how reliable they do so. Our results suggest that under small physiological stressors timing precision and success probability may break first, even if average delays look stable (see Robertson 1993; Van Hook et al. 2020; Reich & Rosenbaum 2012).

This is a minimal, phenomenological single-synapse model, so don't overgeneralize: we omit ion-channel dynamics, dendritic filtering, short-term plasticity and network compensation, and our pH effects are heuristic (probability + variance multipliers). Still, the main point is practical (report variance and reliability), and the next steps are relatively straightforward: reparameterize with patch/slice data, add short-term plasticity or a small recurrent network, and test whether population timing shows the same sensitivity pattern. Similar arguments about the limits of minimal models and the need to integrate slice-level parameters have been made before (Destexhe & Sejnowski 2001; Faisal, Selen & Wolpert 2008).

5. Conclusion

This minimal in-silico study indicates that small, physiologically plausible changes in temperature and extracellular pH produce qualitatively different effects on synaptic timing: modest warming reliably shortens mean synaptic latency (Q10-consistent), whereas mild acidification chiefly reduces release reliability and increases trial-to-trial latency variability with little effect on the mean of successful events. Because many neural codes depend on both temporal precision and event reliability, these results suggest practitioners should report variance and success rates in addition to mean latencies when comparing conditions or datasets. The model is intentionally heuristic, so as to reparameterize from patch/slice recordings, add short-term plasticity and small network dynamics, and validate whether the same sensitivity pattern holds in electrophysiological data.

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