Does Math Matter to Gray Matter?
(or, The Rewards of Calculus).
Philip Holmes, Princeton University
with Eric Brown (NYU), Rafal Bogacz (Bristol, UK), Jeff Moehlis (UCSB),
Juan Gao, Patrick Simen & Jonathan Cohen (Princeton);
Ed Clayton, Janusz Rajkowski & Gary Aston-Jones (Penn).

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The multiscale brain:

**Ingredients:** \( \sim 10^{11} \) neurons, \( \sim 10^{14} \) synapses.

**Structure:** layers and folds.

**Communication:** via action potentials, spikes, bursts.

Sources: www.siumed.edu/~dking2/ssb/neuron.htm#neuron, webvision.med.utah.edu/VisualCortex.html
## Multiple scales in the brain and in math:

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\[1\] ‘Shall I cross the road now?’

\[2\] ‘When should I quit playing the slots?’

\[3\] ‘Should I do a PhD in Math, or Applied Math ... or Neuroscience?’

... or Cultural Studies ...
What neuroscience is and will become:

A painstaking accumulation of detail: differentiation.
Assembly of the parts into a whole: integration.

And what does math do well?

Integration and differentiation!
(This is not just a corny joke.)
Part I: Decisions and behavior, or Making the most of a stochastic process.
(A macroscopic tale: integration)

Underlying hypothesis: Human and animal behaviors have evolved to be (near) optimal.

(Bialek et al., 1990-2005: Fly vision & steering)
A really simple decision task:

“On each trial you will be shown one of two stimuli, drawn at random. You must identify the direction (L or R) in which the majority of dots are moving.” The experimenter can vary the coherence of movement (% moving L or R) and the delay between response and next stimulus. Correct decisions are rewarded. “Your goal is to maximize rewards over many trials in a fixed period.” You gotta be fast, and right!

30% coherence

5% coherence


Courtesy: W. Newsome
An optimal decision procedure for noisy data: the Sequential Probability Ratio Test

Mathematical idealization: During the trial, we draw noisy samples from one of two distributions \( p_L(x) \) or \( p_R(x) \) (left or right-going dots).

The SPRT works like this: set up two thresholds \( 1/B \) and \( B \) and keep a running tally of the ratio of likelihood ratios:

\[
R_n = \left( \frac{p_L(x_n)}{p_R(x_n)} \right) \times \ldots \times \left( \frac{p_L(x_2)}{p_R(x_2)} \right) \times \left( \frac{p_L(x_1)}{p_R(x_1)} \right)
\]

When \( R_n \) first exceeds \( B \) or falls below \( 1/B \), declare victory for \( R \) or \( L \).

Theorem: (Wald, Barnard) Among all fixed sample or sequential tests, SPRT minimizes expected number of observations \( n \) for given accuracy.
Interlude: a mathematical **DDance**:

Take logarithms: multiplication in $R_n$ becomes addition.
Take continuum limit: addition becomes integration.

The **SPRT** becomes a drift-diffusion (**DD**) process (a cornerstone of 20th century physics):

\[
\frac{dx}{dt} = A \, dt + c \, dW
\]

- **drift rate**
- **noise strength**

and $x(t) = \log R$ is the accumulated evidence (the log likelihood ratio). When $x(t)$ reaches either threshold $Z = \log B$ or $-Z$ declare R or L the winner.

**But do humans (or monkeys, or rats) drift and diffuse?**
**Evidence comes from three sources:** behavior, neurons, and mathematical models.
Behavioral evidence: RT distributions

Human reaction time data can be fitted nicely to the first passage threshold crossing times of a DD process.

\[ \text{thresh. } +Z \]

\[ \text{drift } A \uparrow \]

\[ \text{thresh. } -Z \]

Neural evidence: firing rates

Spike rates of neurons in oculomotor areas rise during stimulus presentation, monkeys signal their choice after a threshold is crossed.


Model evidence: integration of noisy signals

We can model the decision process as the integration of evidence by competing accumulators.

\[ dy_1 = [-\gamma y_1 + f(-\beta y_2) + s_1] dt + \sqrt{D} dW_1 \]
\[ dy_2 = [-\gamma y_2 + f(\beta y_1) + s_2] dt + \sqrt{D} dW_2 \]

(Usher & McClelland, 1995, 2001)

Subtracting the accumulated evidence yields a DD process.

\[ \text{pro}_{\alpha} = y_1 - y_2 \]

OK, maybe. But do humans (or monkeys, or rats) optimize?
Optimal decisions redux 1

The task: maximize your rewards for a succession of trials in a fixed period.

Reward Rate: \( RR = \frac{1 - ER}{RT + D} \) (% correct/average time for resp.)

- **Threshold too low**
  - X
  - RT
  - D
  - RT
  - D

- **Too high**
  - $ RT
  - D
  - RT

- **Optimal**
  - $ RT
  - D
  - RT
  - D
How fast to be? How careful? The DDM delivers an explicit solution to the speed-accuracy tradeoff in terms of just 3 parameters: normalized threshold and signal-to-noise ratio $\alpha = Z/A$, $\beta = (A/c)^2$ and $D$.

$$RT = \alpha \tanh(\alpha \beta)$$

$$ER = 1/[1 + \exp(2\alpha \beta)]$$

$$RR = \frac{1 - ER}{RT + D}$$

So, setting $\alpha = \alpha^*(\beta)$ we can express $RT$ in terms of $ER$ and calculate a unique, parameter-free Optimal Performance Curve:

$$RT/(total\ delay) = F(ER)$$
A behavioral test 1

Do people adopt the optimal strategy?
Some do; some don’t.

Is this because they are optimizing a different function, e.g. weighting accuracy more?

Or are they trying, but unable to adjust their thresholds?

A mathematical theory delivers precise predictions. Its successes and failures generate further precise questions, suggest new experiments.
A modified reward rate function with a penalty for errors gives a family of OPCs with an extra parameter: the weight placed on accuracy. (It fits the whole dataset better, but what’s explained?)

Bottom line: Too much accuracy is bad for your bottom line. (Princeton undergrads don’t like to make mistakes.)
Choosing a threshold

Q: Suboptimal behavior could be reckless (threshold too low) or conservative (threshold too high)? Why do most people tend to be conservative? Could it be a rational choice? Which type of behavior leads to smaller losses?

A: Examine the RR function. Slope on high threshold side is smaller than slope on low threshold side, so for equal magnitudes, conservative errors cost less.
Thresholds and gain changes

How might thresholds be adjusted ‘on the fly’ when task conditions change?

Neurons act like amplifiers, transforming input spikes to output spike rates. Gain improves discrimination. (Servan-Schreiber et al., Science, 1990.)

Neurotransmitter release can increase gain. Specifically, norepinephrine can assist processing and speed response in decision tasks, collapsing the multilayered brain to a single near-optimal DD process.
Part II: Spikes and gain changes, or Let them molecules go!
(A microscopic tale: differentiation.)

Underlying hypotheses:
Threshold and gain changes in the cortex are mediated by transient spike dynamics in brainstem areas. Transients determined by inherent circuit properties and stimuli.

(Aston-Jones & Cohen, 1990-2005.)
**A tale of the locus coeruleus (LC)**

The LC, a neuromodulatory nucleus in the brainstem, releases norepinephrine (NE) widely in the cortex, tuning performance. The LC has only ~30,000 neurons, but they each make ~250,000 synapses. Transient bursts of spikes triggered by salient stimuli cause gain changes, thus bigger response to same stimulus.

Devilbiss and Waterhouse, *Synapse*, 2000

In waking animals, the LC ‘spontaneously’ flips between two states: tonic (fast average spike rate, poor performance) and phasic (slow average spike rate, good performance).

Transients are crucial: the LC delivers NE just when it’s needed.
Hodgkin & Huxley (J. Physiol., 1952) developed a biophysical model of a single cell. Charged ions pass through the cell membrane via gates. Electric circuit equations + gating models fitted to data describe the dynamics. The HH model (for squid giant axon) has been generalized to many types of neurons. It’s a keystone of neuroscience; it describes the spikes beautifully, but the equations are really nasty!

\[
\begin{align*}
\dot{v}_i &= [I_i^b - g_{Na}m_{\infty}(v_i)^3(-3(q_i - Bb_{\infty}(v_i)) + 0.85)(v_i - v_{Na}) \\
&- g_{K}q_i(v_i - v_{K}) - g_{L}(v_i - v_{L}) + I_i^{ext}] / C \\
\dot{q}_i &= (q_{\infty}(v_i) - q_i) / \tau_q(v_i)
\end{align*}
\]


However, ……
LC cells are spontaneous spikers and we can use this to reduce the HH equations to a simple phase model.

Modeling LC neurons 2

In phase space, periodic spiking is a closed curve:

So we may change to 'clock face' coordinates \( \theta \) that track phase -- progress through the firing cycle -- and by marking time in a nonuniform manner, we collapse HH to simply:

\[
\theta = \omega + \text{external inputs}
\]
Well, it’s not quite that simple: External inputs, stimuli and synaptic coupling from other cells, are all ‘filtered’ through the phase response curve (PRC), which describes inherent oscillator properties:

\[
\dot{\theta} = \omega + Z_V(\theta)[\text{inputs}]
\]

but given this, we can compute their effects.

And we can find the PRC:

\[
Z_V(\theta) = \frac{c}{\omega}[1 - \cos \theta]
\]

(external stimuli speed up the spikes most at 9 o’clock)
Modeling LC neurons 4

There are many such oscillating ‘clocks’ in LC, and the stimulus reorders and coordinates their random phases.

\[ \omega = 3 \text{Hz} \quad \quad \omega = 1 \text{Hz} \]

Tonic LC: fast on average, gives a small burst.

Phasic LC: slow on average, gives a big burst.

The size of this effect depends upon the intrinsic frequency.
Modeling LC neurons 5

Adding noise and weak coupling, we can match the experimental PSTH data.

After stimulus ends, noise and random frequencies redistribute the phases.
Matching the PSTHs reveals that intrinsic frequency and its variability and stimulus duration are key parameters.

1. Slower oscillators deliver bigger coherent bursts.
2. Burst envelopes decay exponentially.

The latter may be responsible for attentional blink.  (Niewenhuis et al., J. Exp. Psych. 2005.)
Summary and Morals

1. Neural activity in simple decisions is like a DD process:
   the model predicts optimal speed-accuracy tradeoffs.

2. Threshold adjustments can optimize rewards.

3. The LC-NE system provides a control mechanism:
   the model reveals roles of intrinsic vs. stimulus properties.

4. There’s very pretty mathematics at all scales:
   stochastic ODE, dynamical systems, freshman calculus.

5. Large gaps remain: we must bridge the scales.
   Morals: Good mathematical models are not just (reasonably) faithful; they’re also (approximately) soluble. They focus and simplify.

Thanks for your attention!
Learning a threshold

An algorithm based on reward rate estimates and a **linear reward rate rule** can make rapid threshold updates by iteration.

But … Can RR be estimated sufficiently accurately?

Can the rule be learned?

Does noise cause overestimates?

(Simen et al., 2005.)