Using Virtual Patients to Predict Perceptual Performance after Optogenetic Sight Recovery

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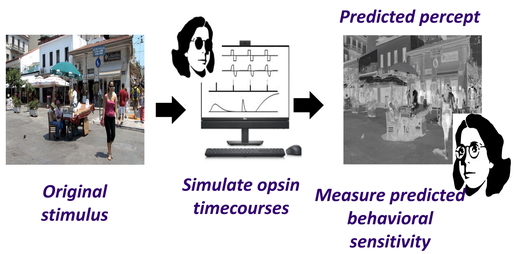
1. The Virtual Patient

Predicting the Perceptual Experience of Optogenetic Vision

Optogenetic sight recovery uses retinaldehyde-binding proteins to elicit light sensitivity in remaining healthy retinal cells (bipolar and/or ganglion cells) of patients with inherited retinal disorders.

Can we predict functional vision from cell responsiveness?
Opsins vary in sensitivity and speed which cause perceptual distortions. Here, we show how a 'virtual patient' can be used to predict the perceptual performance of optogenetic vision [1].



Model photocurrents for three optogenetic proteins (ChR2, ReaChR and ChRmine)

Measure contrast detection thresholds for natural vision & simulated optogenetics

Metric: Temporal Contrast Sensitivity Function (TCSF)

Experiment: 2AFC orientation discrimination (+/- 45°) for Gabors
Spatial frequency: 0.5 - 16 cpd
Temporal frequency: 1.5 - 20 Hz

2. Modeling Photocurrents for Three Opsins

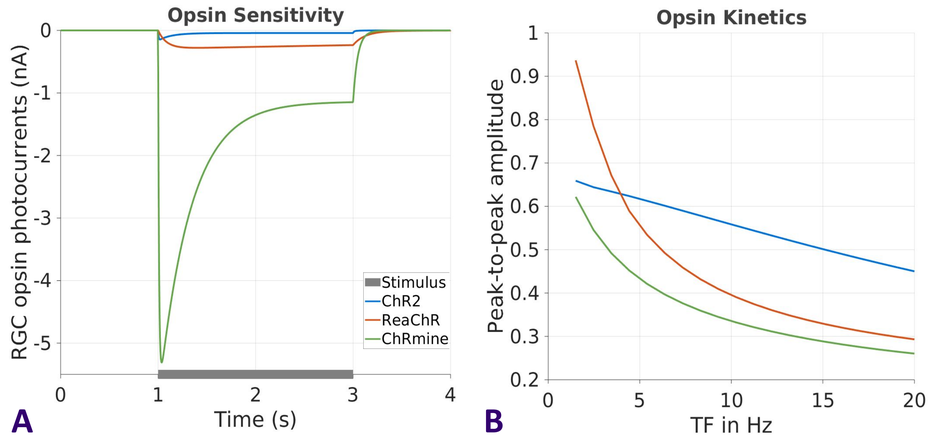


Fig 1. (A) Opsin sensitivity is determined by the photocurrent response to a 1-second light stimulus at an irradiance of 1 mW/mm² for (i) ChR2 (ii) ReaChR and (iii) ChRmine. (B) Opsin speed is quantified by the peak-to-peak amplitude of the photocurrent response to sinusoidal stimuli at increasing temporal frequencies, where slower opsins exhibit a rapid attenuation. Data are based on photocurrent models of optogenetic responses in microbial opsins[2].

3. Simulated Optogenetic Timecourses

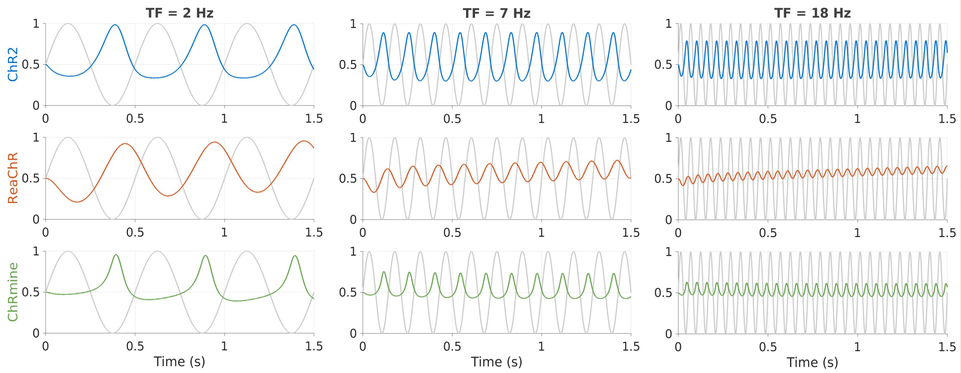


Fig 2. In a 2AFC orientation discrimination task, contrast levels of Gabor gratings were sinusoidally modulated over time (control condition in grey) and then passed through optogenetic filtering to simulate response kinetics of (i) ChR2 (ii) ReaChR and (iii) ChRmine. Optogenetic responses were normalized to begin at the same contrast level and to reach the same peak value at the lowest TF.

4. TCSF Detection Thresholds

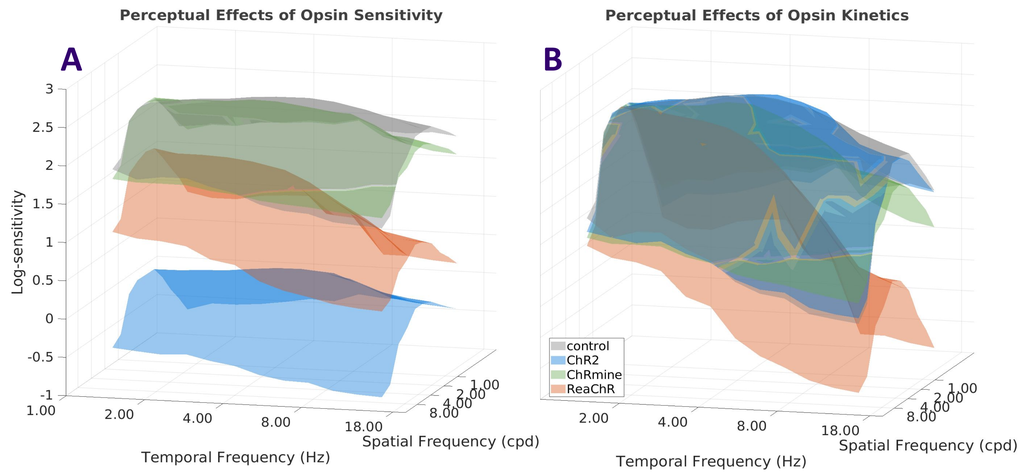


Fig 3. TCSFs of simulated optogenetic responses measured by the 2AFC orientation discrimination task using virtual patients for (i) neurotypical vision (ii) ChR2 (iii) ReaChR and (iv) ChRmine. (A) Unscaled TCSFs highlight differences in perceptual sensitivity between opsins and control. A larger deviation from the neurotypical TCSF reflects greater loss of visual acuity. (B) TCSFs (scaled to match peak sensitivity of controls at lowest TF) illustrate the effect of opsin kinetics. The slope of the curve shows how rapidly sensitivity declines with increasing TF, with steeper slopes indicating stronger attenuation of high-frequency signals.

5. Discussion

Both Speed and Sensitivity matter!

- Our framework can be used to predict perceptual performance of any opsin.
- **ChR2:** Fastest opsin - matches neurotypical attenuation of higher TFs most closely, reducing temporal distortions. However **its low sensitivity leads to a ~100x loss of visual acuity**.
- **ReaChR:** More sensitive than ChR2: ~30x improvement in visual acuity at the lowest TF. However, it has steep drop-off in sensitivity above 5 Hz (corresponds to a 10x loss in sensitivity between 5 Hz and 16 Hz) **rendering fast moving objects invisible. Losses are likely to be more severe in the presence of eye-movements.**
- **ChRmine:** Most sensitive of the three opsins. Attenuates higher TFs at ~2x more than neurotypical vision leading to more suppression of fast moving objects. **Could potentially preserve spike fidelity when used with light-amplifying goggles.**

REFERENCES
[1] Fine, Boynton 2015. Pulse trains to percepts: The challenge of creating a perceptually intelligible world with sight recovery technologies. Philosophical Transactions of The Royal Society B Biological Sciences. (DOI: 10.1098/rstb.2014.0208)
[2] 1. Bansal, H., Gupta, N. & Roy, S. Theoretical analysis of optogenetic spiking with ChRmine, bReaChES and CsChrimson-expressing neurons for retinal prostheses. J. Neural Eng. 18, 0460b8 (2021).

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