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**Title:** Comparison of adaptive psychophysical methods for the use of nociceptive threshold tracking; a simulation and human subject study.

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**Abstract: Introduction:** Nociceptive thresholds show dynamic changes during noxious events such as disease, clinical intervention or experimental perturbations. Tracking psychophysical thresholds before, during and after a nociceptive conditioning stimulus might provide insight in both ascending and descending nociceptive pathways. Tracking of thresholds requires efficient selection of test-stimuli such that accurate estimations can be made on a short time interval and with few stimuli. This study aims to compare stimulus selection methods in terms of bias, precision, efficiency and bandwidth.

**Simulations:** Monte Carlo simulations were performed to compare a simple staircase method, PSI method and a random staircase method. A stochastic psychophysical model was applied to simulate responses to selected stimuli assuming a fixed or a step-wise changing threshold. Results showed that the random staircase estimation method quickly converged to the true threshold with a small set of stimuli and corresponding responses. However, the staircase and PSI methods performed similarly. Both staircase methods showed higher precision than the PSI method and appear to be more efficient than the PSI method. The staircase method quickly responds to the change in threshold, but with overestimation, the PSI method responds very slowly to the change in threshold and the random staircase method responds quickly, but slower than the staircase, and shows no overestimation.

**Human subject experiments:** Both the staircase and random staircase method were compared in psychophysical experiments including 35 healthy human subjects. Electrical test-stimuli were applied using a needle electrode attached to subjects’ left forearm. During the experiment, stimuli were given at a frequency of 0.5-1.5Hz. Subjects were instructed to indicate perceived stimuli. A cold pressor task was used as a nociceptive conditioning stimulus. The experiments contained two parts; 1) static: 10 minutes of threshold tracking, and 2) dynamic: 23 minutes of threshold tracking with a cold pressor task between the fifth and eighth minutes. Results showed a trend in static thresholds over time. With static data, the random staircase showed to have a higher precision and higher efficiency. Moreover, no significant difference was found in threshold estimations in the dynamic part. However, a change in thresholds occurred due to the cold pressor task.

**Conclusion:** We simulated three stimulus selection procedures and found that the simple staircase and random staircase methods performed better than the PSI method. Within human subjects, we found the random staircase method to be more efficient in tracking thresholds.