TāStation®: A New High Throughput Technology for Precise Measurement of Human Taste

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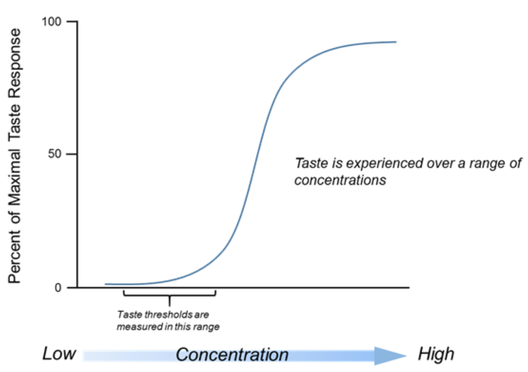
ABSTRACT

We have invented and developed a fully automated high throughput technology for human taste measurement called the TāStation®. The system is comprised of an automated sample delivery mechanism and a touch-sensitive display (TSD) which both guides subjects through their tests and serves as the medium for recording their responses. Subjects are trained by an interactive game-like algorithm to associate the tastes of control standards with specific coordinates on the TSD. Tastant solutions are dispensed in a 96-well plate placed on an x-y motion table beneath an electronic pipette mounted on a z-axis gantry. On each trial, a small volume (0.2 ml) is drawn from a single, randomly selected well. The pipette then is presented to the subject, who in turn manually administers the sample to the tongue. On control trials, responses made by touching the TSD are occasioned by a positive or negative consequence—if the touch is made within the appropriate target coordinates a virtual poker chip (with remunerative value) appears, and if outside the target a point-reduction/time-out penalty occurs. All responses on trials presenting novel taste stimuli are rewarded regardless of the location. A trial is thus defined by the sequence of sample presentation, tasting, TSD response, and consequence. Subjects complete a 96-trial session in ~40 minutes with high performance accuracy and test-to-test reproducibility. The software is designed to exploit the experimental flexibility inherent in the 8x12 matrix of the 96-well plate so that a large array of test protocols can be operated under the interactive algorithms. The TāStation® has been used successfully to conduct rapid screening of tastant libraries, perform concentration-response analysis of multiple tastants simultaneously, and determine threshold sensitivities and taste phenotypes of individual subjects with unprecedented precision. The TāStation® therefore represents a breakthrough technology with many applications for sensory science.

TASTE AS A FUNCTION OF CONCENTRATION 1

The intensity of the taste of any chemical is a function of its concentration. Although concentration-dependence can be suggested by measuring taste responses at the lowest "threshold" concentrations, only by establishing the ***concentration-response function*** can the full effect of tastants as sensory stimuli be fully appreciated and rigorously evaluated. For example, taste responses at threshold concentrations provide little, if any, insight regarding the taste sensations resulting from the high concentrations of a tastants normally encountered in food, beverages, or liquid medications.

The Concentration-Response Function Provides a Thorough and Rigorous Representation of Taste



Concentration-response Functions and EC50s: The EC50, derived from a curve fit to the data by non-linear regression, represents the concentration of each tastant that elicits a half-maximal taste response and is a convenient metric for estimating placement of the concentration range in which the compound is taste-active.

Approximating the Maximal Taste Response from the Concentration-response Function: The top of the curve in the figure represents the approximate maximal taste response. The plateau of the curve is due to saturation of tastant receptors. At the lowest concentrations the tastant solution becomes difficult to distinguish from water, and therefore provides a reliable estimate of the taste threshold.

AUTOMATED SYSTEM FOR HIGH THROUGHPUT MEASUREMENT OF HUMAN TASTE 2

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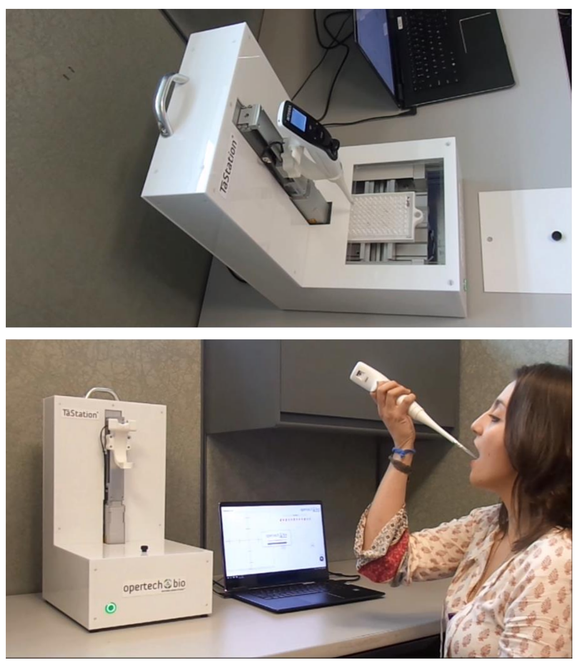

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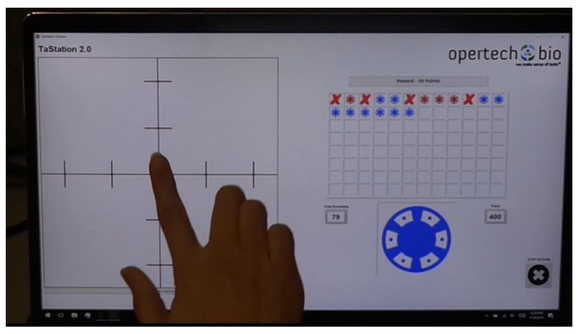

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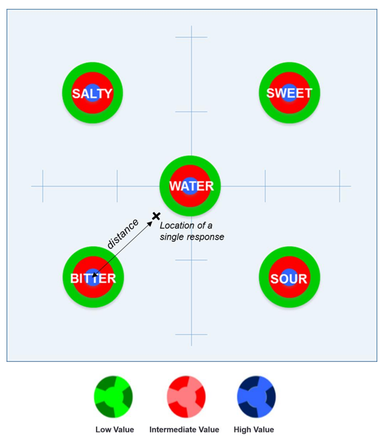
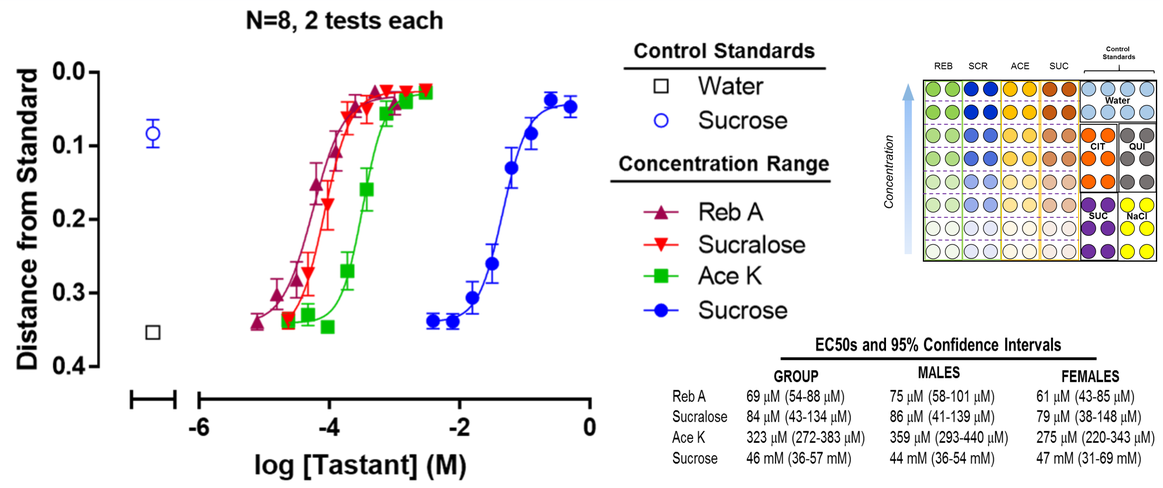


A) Robotic gantry moves an automated pipette over a 96-well plate. The pipette is lowered into a randomly selected well and withdraws a fixed volume of 200 ul. The subject is instructed by the algorithm to remove the pipette and self-administer the content of the pipette to the tongue.
B) Subjects search for poker chips buried in a visual field; the taste stimulus is a clue to their location. The subject touches the screen at a location guided by the taste of the antecedent stimulus. Response-reinforcement contingency is absolute on control trials (taste standards). On test article trials—those for novel stimuli—all responses are reinforced.
C) The distance between the coordinates of the subject's response and the ideal coordinates of the target is measured and recorded as the datum.

<u>CONCLUSION:</u> The TāStation® was designed to have the throughput capacity for generating robust concentration-response data. The small volumes and the performance incentive help to minimize or eliminate taste desensitization, allowing a subject to effectively test many samples in a short period of time. Since so much data is generated by each subject in a test session, fewer subjects are needed for statistical power than is the case for traditional taste panels. Furthermore, the incentive structure of the game-like testing approach tends to reduce the variability of responses to replicate trials both within and across test sessions, resulting in a more reliable and repeatable dataset. The data obtained by use of the TāStation® are readily amenable to mathematical curve-fitting techniques such as non-linear regression mentioned above with all the attendant benefit for analysis of concentration-response functions for taste. Furthermore, the ability to effectively evaluate small sample sizes afforded by the TāStation® technology permits the cost-effective evaluation of ingredients that might be expensive or in short supply, such as novel natural products. The TāStation® technology also is ideal for rapid screening of ingredient libraries for taste properties of interest.

RAPID GENERATION OF CONCENTRATION-RESPONSE FUNCTIONS FOR FOUR SWEETENERS 3

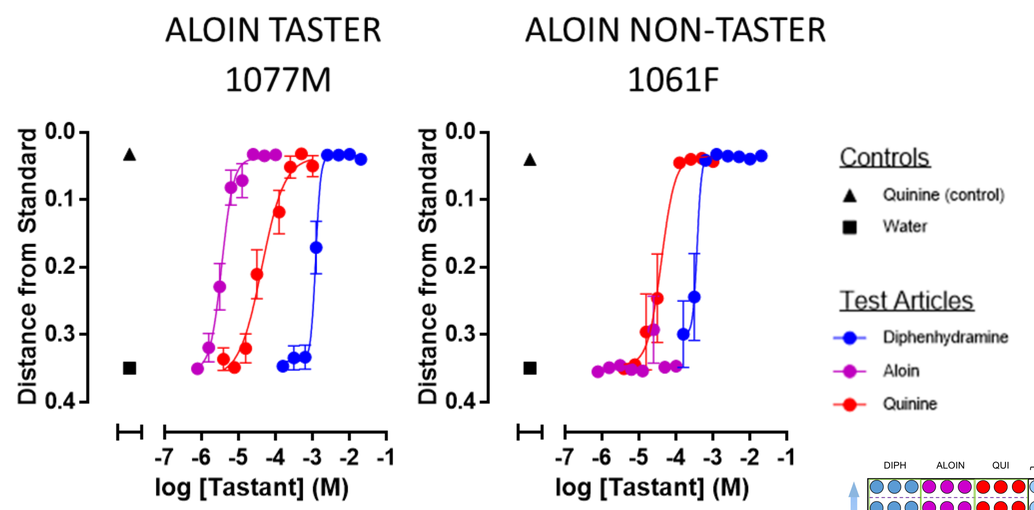


EC50s and 95% Confidence Intervals

GROUP	MALES	FEMALES
Reb A	69 µM (54-88 µM)	75 µM (58-101 µM)	61 µM (43-85 µM)
Sucralose	84 µM (43-134 µM)	86 µM (41-139 µM)	79 µM (38-148 µM)
Ace K	323 µM (272-383 µM)	359 µM (293-440 µM)	275 µM (220-343 µM)
Sucrose	46 mM (36-57 mM)	44 mM (36-54 mM)	47 mM (31-69 mM)

Concentration-response functions for sweet taste stimuli. A cohort of 4 male and 4 female adult subjects was trained and tested as described in Figure 2C. Data are plotted as described in the figure above except that among the control standards, only data for sucrose and water are shown. Curves were fit to the data points by non-linear regression to generate concentration-response function for each of the tastants. EC50s were derived from the curve fits.

BITTER TASTE: CONCENTRATION-RESPONSE FUNCTIONS FOR INDIVIDUAL SUBJECTS ARE CONSISTENT ACROSS TESTS 4

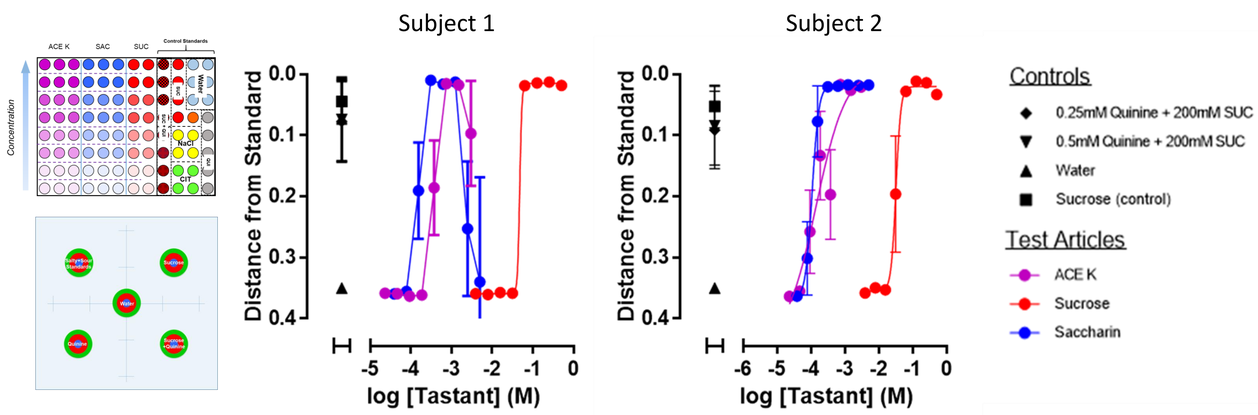


SUBJECT 1077 M

Test Date	12/5/2017	12/12/2017	3/10/2018	3/12/2018	3/13/2018	3/14/2018
	EC50 (mM)					
DIPHENHYDRAMINE	1.2	1.4	1.2	1.3	1.3	0.71
QUININE	0.05	0.06	0.03	0.11	0.05	0.07
ALOIN	0.003	0.006	0.003	0.014	0.003	0.004

Bitter taste concentration-response functions for individual taster and non-taster subjects. Data are plotted as described above for one aloin taster and one non-taster. Each data point represents the average of 6 replicates (3 replicates x 2 tests). In the table below, EC50s are given for 6 consecutive test sessions for subject 1077M.

PHENOTYPE-DEPENDENT SENSITIVITY TO BITTER TASTES IMPARTED BY NON-NUTRITIVE SWEETENERS: CONCENTRATION-DEPENDENCE 5



Subjects were trained to discriminate pure sweet from bittersweet, pure bitter, water, salty, and sour taste standards by associating their tastes with specific coordinates on a touch sensitive display (***Inset***). In test sessions, subjects' responses were recorded on targets associated with pure sweet, bittersweet, and pure bitter as a function of concentration. Control standards were also included in every test session. The data shown are from individual subjects, one male and one female each from aloin taster and non-taster phenotypes, each tested twice.

PHARMACEUTICALS CAN BE SAFELY EVALUATED AND SCREENED AGAINST LIBRARIES OF PUTATIVE BITTER BLOCKERS 6

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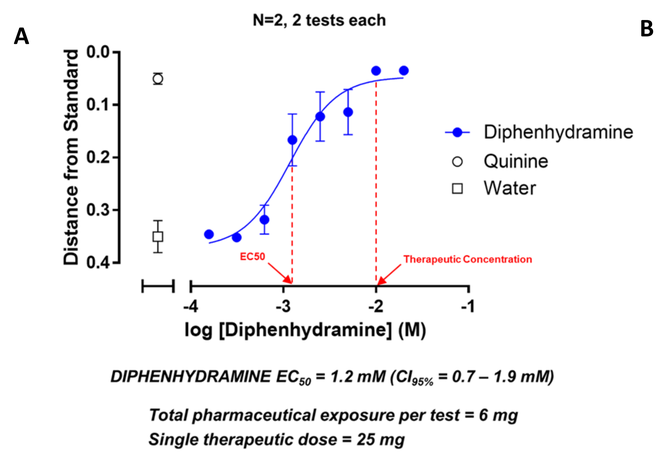

DIPHENHYDRAMINE EC_{50} = 1.2 mM ($CI_{95\%}$ = 0.7 – 1.9 mM)

Total pharmaceutical exposure per test = 6 mg
Single therapeutic dose = 25 mg

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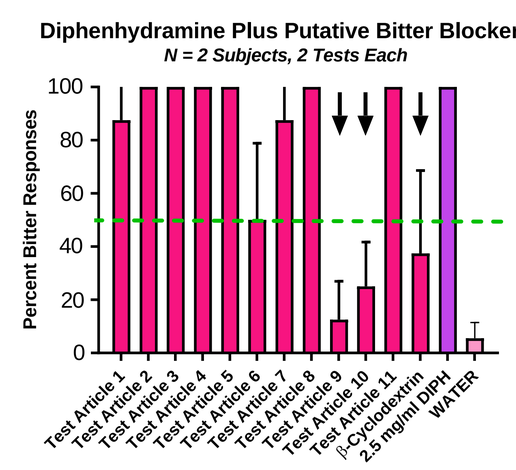

A) Concentration-response function for bitter taste of the antihistamine diphenhydramine. *One* male and one female adult subject each was tested twice to generate the concentration-response function shown. Data are plotted as the distance from the ideal coordinates for the bitter standard (0.5 mM quinine). Each data point in the curves was calculated as the average across 12 replicates (3 replicates per concentration x 2 tests x 2 subjects). **B) Screening for bitterness mitigation against a therapeutic concentration of diphenhydramine. A) E**ach subject was tested twice in a binary "bitter vs. non-bitter" procedure. Each putative bitter blocker was tested at a single concentration (recommended by the vendor or as indicated in the scientific literature) added to 2.5 mg/ml diphenhydramine. Data are plotted as the percentage of trials on which subjects indicated a bitter response. Each test article was replicated 4 times per plate, each plate was tested twice by each subject (total 16 trials per test article). Dashed green line indicates arbitrary cut-off for "hit" selection; black arrows indicate "hits."