DEVELOPMENT AND VALIDATION OF A PORTABLE DEVICE FOR AT-HOME HYDROGEN AND METHANE BREATH TESTING

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Aims

- Develop a portable, sensor-based breath testing device for hydrogen and methane
- Develop a platform to simulate human breath to test the accuracy of the device
- Compare the device with currently available hydrogen and methane analyzers to benchmark the performance for future applications

Background and Objectives

Hydrogen and methane breath tests (HMBTs) can be used in the clinic to diagnose small intestinal bacterial overgrowth (SIBO) and carbohydrate malabsorption (CM) due to the connection between the levels of these gases in the breath and the activity of the gut microbiome (1). The North American Consensus Guidelines provide a standardized process for the optimal interpretation of HMBTs when they are used to support a diagnosis, and such guidelines are informed by experimental work and expert opinion by a consortium of specialists (2,3).

Longitudinal measurement of hydrogen and methane, as opposed to a single samples allows monitoring of treatment response and early detection of recurrence. OMED Health™ has developed a portable hydrogen and methane breath analyzer device for this purpose (Figure 1). The data generated from the device is immediately available to medical professionals. The premise of home monitoring devices is to repeatedly use them, and so they must be as accurate as possible. It is well known that water vapor and interfering volatile compounds such as acetone and isoprene can cause loss of accuracy and precision (4,5), and therefore the OMED device has been designed with a fitering mechanism to address this.

We have undertaken several validation tests to measure the accuracy of the OMED breath analyzer device. We have developed a gas concentration predictive model, simulating human breath and allowing us to measure the concentration of hydrogen and methane within a complex mix of on breath gases from multiple sensor readings across a range of temperatures and humidities. We also benchmarked the OMED breath analyzer to an in clinic hydrogen and methane analyzer, the Gastrogenius™ Breath Monitor (HMBT), using the breath of human volunteers.

Synthetic Breath Testing

941 synthetic breath exposures were included in a training set across a range of concentrations, temperatures and humidities. The desired concentrations of hydrogen and methane were generated by calculating the required ratios of constituent supply gases (shown in Figure 2) in a synthetic breath gas flow. The synthetic breath is humidified using a set of Dreschel Bottles and controlled by changing the ratio of dry to humid constituent gases. Environmental temperature was controlled using an environmental test chamber unit. Artifacts in the flow controllers (i.e. overshoots) were smoothed out by diverting the flow through a solenoid valve system. The Gas flow is then divided equally between multiple devices to allow for simultaneous testing by balancing the downstream pressures at the exhaust of the rig. In-process checks were used to continuously monitor the delivery of gases and the environmental control.

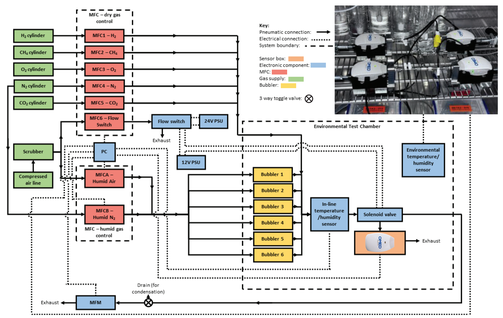

Figure 1: Schematic of the synthetic breath platform.

The gas concentration predictive model sits at the heart of the OMED devices allowing the measurement of the concentration of hydrogen and methane from multiple sensor readings. With enough data from the breath, the device is able to generalize the relationship between gas sensors to make an assessment of the underlying concentrations of hydrogen and methane across a range of temperatures and humidities. The synthetic breath part of training data collect was delivered on a range of set hydrogen and methane concentrations (Figure 3). The distribution of exposures were selected to closely match what was observed in real patients clinical breath samples. Good temperature and humidity control were observed throughout training data collect, and stabilization periods were adequate. The data collected from the training data was of good quality for the purposes of developing the model.

References

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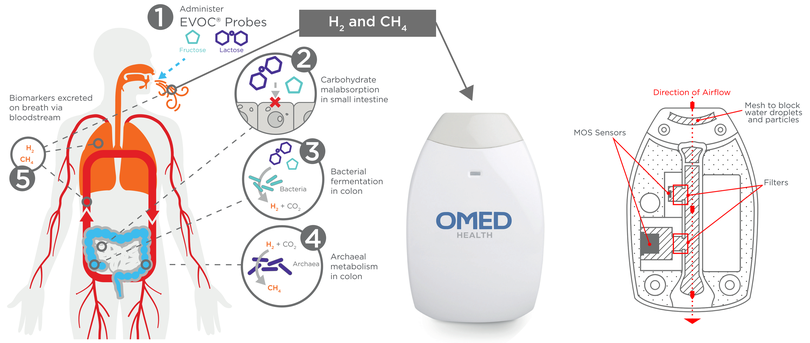

Figure 2: The OMED Health Breath Analyzer device. The OMED Health device uses MOS sensor-based technology to analyze the levels of hydrogen and methane in the breath (patent pending). It is portable, and can provide information on the go. A diffusion membrane acts as a filter between the main flow path and the sensor chamber to negate the impact of interferant breath VOCs on the sensor response. A mesh (PTFE membrane) prevents moisture from condensing on the sensors and impacting the sensor baseline.

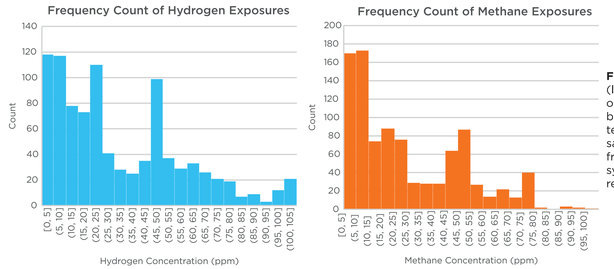

Figure 3: Histograms of hydrogen (left, blue) and methane (right, orange) concentrations in synthetic breath exposures used to train and test the model. Concentrations sampled from HMBT dataset drawn from real world data, to acquire synthetic data at a distribution reflecting a clinical population.

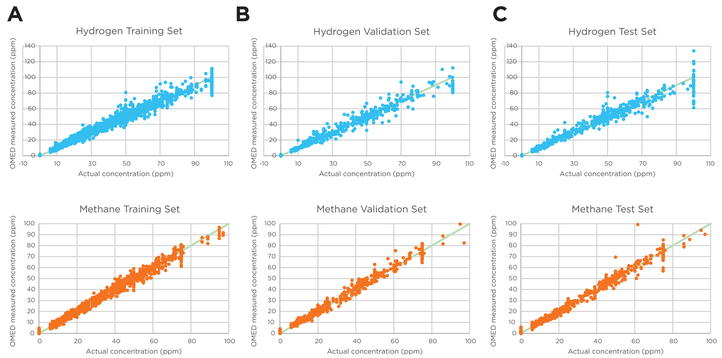

Figure 4: Analytical modelling of the OMED device. based on sensor-response to synthetic breath. A: Model prediction accuracy for Training, B: Validation, C: and Test datasets.

The total data was split in 3 datasets (Training 60%, Validation 20%, Test 20%) to test the accuracy of the device to measure hydrogen and methane. The analytical model was trained on the training dataset (A), and fine-tuned on the validation dataset (B) according to industry standards and best practice. The test dataset was never seen by the analytical model during development, and therefore gives a good estimate of the capability of the model to accurately assess hydrogen and methane levels in breath. This data indicated that the sensors in the OMED device and analytical model utilized as part of the device can accuractely assess and report hydrogen and methane levels. Next, the OMED device was compared to a clinically-validated HMBT that is used to provide hydrogen and methane levels in the breath that can be used for diagnostic purposes (Figure 5).

Human Breath Testing

Study Cohort and Breath Sample Collection: A total of **243 breath samples** were collected from **54 participants.** Each participant gave two back-to-back samples (3min interval) into the HMBT instrument, and a mean of two measurements from the HMBT was calculated (AVG) as assumed ground truth of breath concentration. Inbetween, the participants gave a breath sample into the OMED device. The results of the AVG HMBT measurements were then compared with the values from the OMED device for both hydrogen and methane.

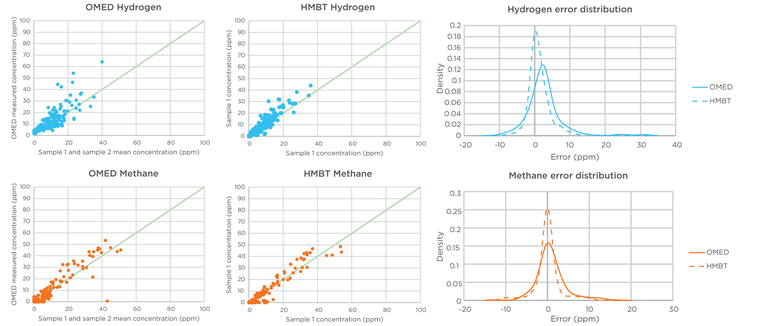

Figure 5: Comparison of a clinical HMBT and the OMED device. The left two graphs are a comparison of the mean (AVG) of the two HMBT measurements compared to the OMED device. The middle two graphs are a comparison of the first HMBT measurement to the second measurement. The right two graphs show the distribution of errors between the AVG from clinical HMBT and OMED device for hydrogen (top) and methane (bottom).

The calculated error of the two HMBT measurements taken in rapid succession is shown for both hydrogen and methane are shown (Figure 5). This shows how much error can be expected in a benchmark for the OMED device. An average of these two values (AVG) was taken as "ground truth" for the following analysis. The OMED device was then compared to AVG, and the error calculated. This showed that there was a comparable error for hydrogen and methane.

The distributions of the error measurements on hydrogen and methane measurements was then shown in Figure 6. This showed that there is a slight positive bias in hydrogen measurements using the OMED device vs the HMBT. However, as the diagnostic criteria outlined in guidelines compare the difference in later time points of hydrogen to baseline, this reduces the impact of any bias, compared to a single cut-off value and was further investigated.

The confusion matrices (Figure 6) show diagnostic results for SIBO/IMO tests performed with standard HMBT test and with the OMED device, in parallel; the results show the number and proportion of tests that have the same or different outcome. A high degree of concordance can be observed between HMBT- and OMED-based diagnoses, with the only discrepancies being 1 IMO false negative and 1 SIBO false positive. A preliminary study has shown that patients might not strictly adhere to the samples timings, which could result in false positive SIBO diagnoses due to delayed samples when using standard HMBT. OMED offers a significant advantage by accurately timestamping the samples, together with an appropriate in-app test workflow, that can increase test accuracy.

SIBO positive diagnoses are based on an increase of at least 10 ppm on the baseline hydrogen concentration within 65 minutes of lactulose ingestion, and IMO positive diagnoses are based on the presence of any sample during the test exceeding 10 ppm. Not all SIBO tests could be included in the results because of missing samples.

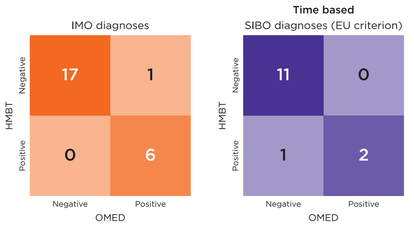

Figure 6: Diagnostic performance of the OMED Device is virtually equivalent with the gold-standard HMBT testing for both SIBO and IMO, with an accuracy of >90% for IMO and SIBO (EU criterion). This means that if OMED alone was used to diagnose SIBO and IMO, in more than 90% of cases the diagnosis would have been the same as the one derived from the HMBT test results.

Conclusion

Taken together, this data suggests that the OMED device is highly accurate with a comparable performance to an in-clinic HMBT. The added portability for convenience, and possibility of taking regular at-home measurements can provide significant benefit for users by providing longitudinal data that is immediately available to their health care provider.