TB-screening by exhaled-breath analysis using mass-producible electronic noses

Tuberculose Diagnostiek Dagen 2013

RIVM Bilthoven, 20 juni 2013

National Geographic News--Dogs Smell Cancer in Patients' Breath, Study Shows

Stefan Lovgren for National Geographic News January 12, 2006

"Dogs can detect if someone has cancer just by sniffing the person's breath, a new study shows.

Breath Diagnostics Opportunity

- Breath diagnostics
  - Rapid, low-cost, mass producible, screening device
  - Non-invasive
  - No alternative screening methods available for some applications

- Indications
  - **Tuberculosis**
  - Cancer
  - COPD, asthma
  - Lung transplants
  - Heart failure / angina pectoris
  - Diabetes
  - ……..

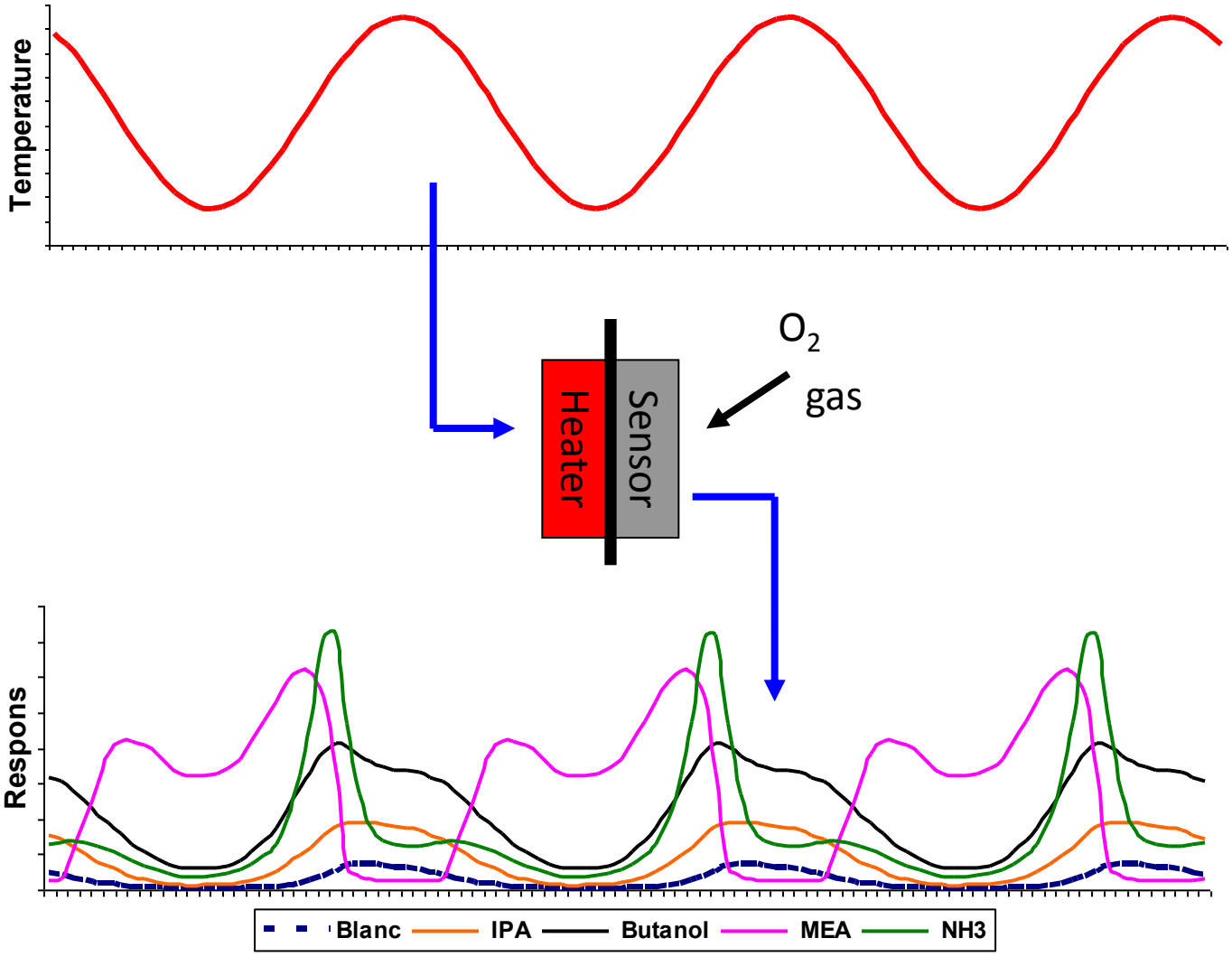
WHO-FIND report “Diagnostics for Tuberculosis” page 81

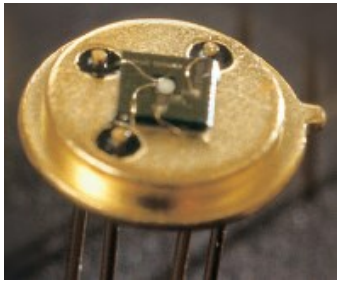
	SPUTUM MICROSCOPY		SPUTUM CULTURE		SCREENING TEST	
Dimension	**Current benchmark**	**Replacement test**	**Current benchmark**	**Replacement test**	**Current benchmark**	**Replacem test**
Intended use	Detect advanced, contagious TB		Detect early or extrapulmonary TB		Rule out TB in suspects	
Specimen type	sputum	blood, urine, saliva, sputum, breath	sputum	blood, urine, saliva, sputum, breath		blood, urine, saliva, sputum, breath
Specimen number	3	1	3	1		1
Sensitivity	40–70% sputum; <20% other	50–70%	80–90%	80–90%		95%
Specificity	> 95%	> 95% = culture	> 95%	> 95%		60%
Performance reduced in HIV+ cases	yes	yes/no	yes	yes/no	no existing assay	yes/no
Speed	2 hours–7 days	< 3 hours	4 weeks	< 7 days		< 3 hours
Infrastructure needs	light microscope	simpler than microscopy	multi-step processing + incubation	minimal processing, electricity		minimal
Technician requirements	moderate	minor	moderate	minor		minimal
Stability	3 months–	1–2 years	3 months	1–2 years		1–2 years

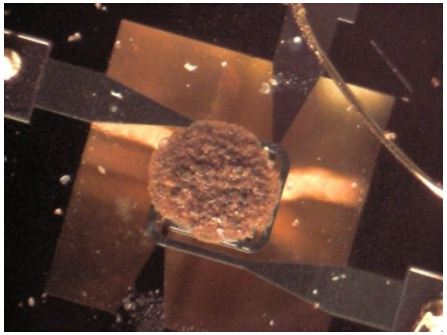
Our approach to eNose technology

- Mass producible, low-cost hardware, rugged
- Avoid chemical calibration of individual devices
  - Device independent calibration models
  - Develop calibration model once, roll out over all devices

MOS Temperature cycling

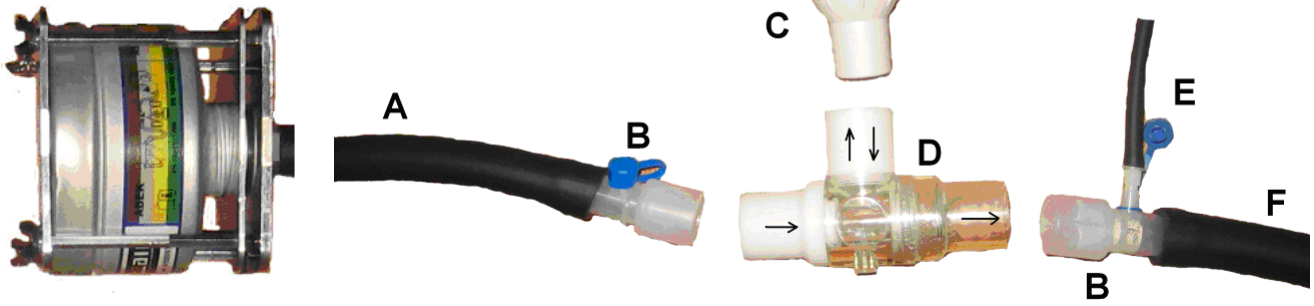




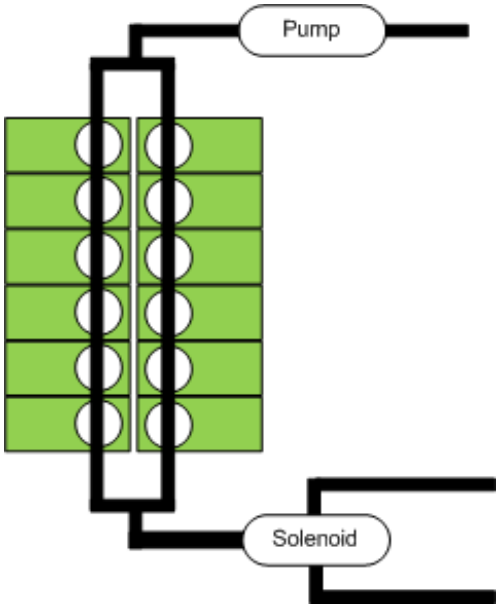


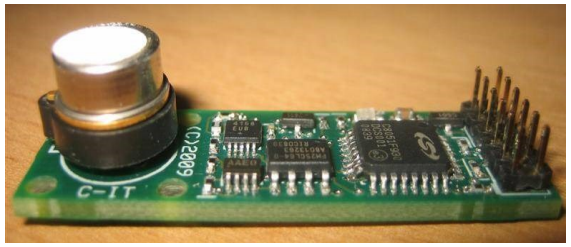
Sample collecting

- Remove ambient interferents
- Collect sufficient sample for duplicate



Measurement Setup - DiagNose II





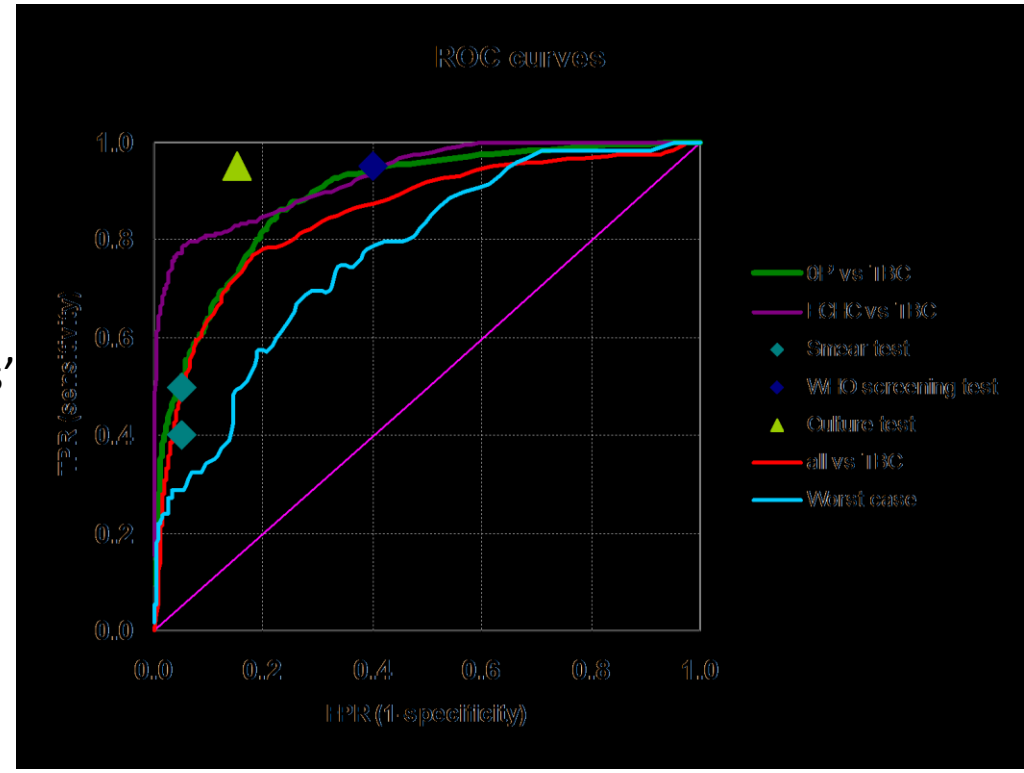
- 4 sensor types in triplicate
- Virtual devices

Collected data set

- Most measurements in duplicate over 2 days
- TBC classification based on reference standards
    - Smear test (3x)
    - Solid culture
- Total data set 326 measurements
    - 59 TBC
    - 182 ‘otherwise sick’
    - 36 socio-economic control
    - 49 employee control

Proof of Principle in Tuberculosis

- Bangladesh study
  - 200 patients
  - 1 site
  - Completed (2010)
  - Paper published in ‘Tuberculosis’
- Results
  - Achieved primary goals
  - High specificity
  - High sensitivity



How golden is the reference?

- Smear test
  - Estimated 90-95% specificity
  - Estimated 40%-50% sensitivity
- Solid culture
  - Estimated 95% specificity
  - Estimated 85% sensitivity

- There are false positives and false negatives in our data set!
  - Complicates data analysis enormously
- Non-open/extra-pulmonary TB?
  - E-nose may pick up VOC's from blood stream
  - How many of the 'otherwise sick' have other form of TB?

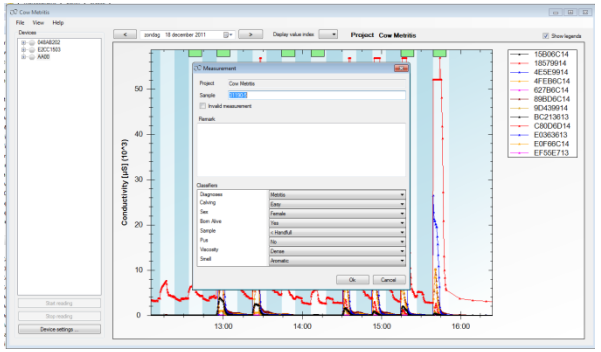
Proposal for next steps

- ‘Rock-solid’ data required for improved calibration model
- Complete a repeat study in EU
- Using dedicated eNose
- Collaboration with RIVM, GGD, ‘ter Apel’, Beatrixoord, ...
- Studies abroad (Kenya, Yogyakarta, ...)
- Healthy control groups required.

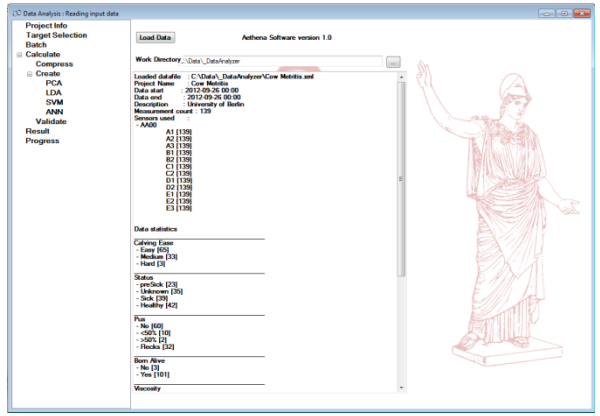
Aeonose

Advanced data analysis

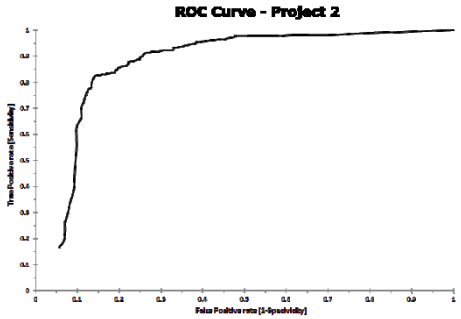
capturing



data compression and analysis



presenting



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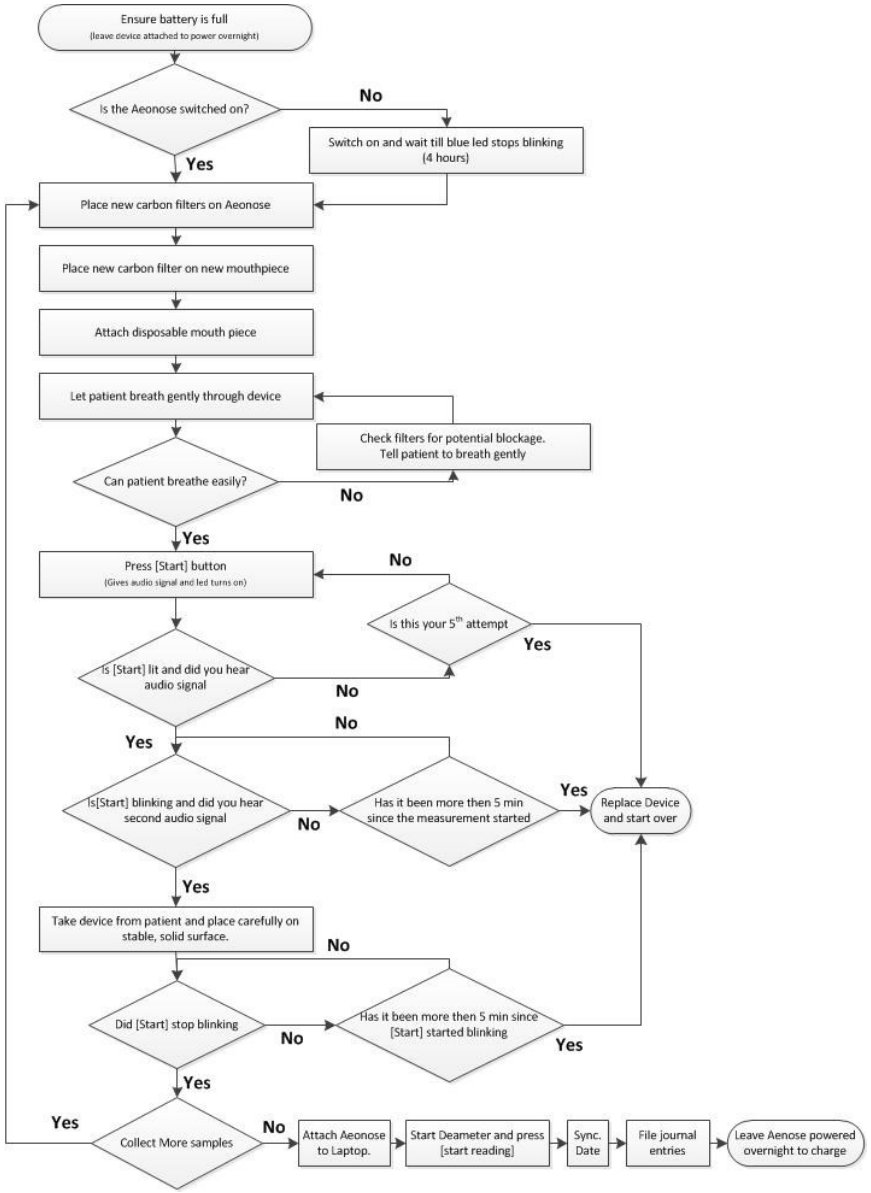
Test protocol



Questionaire

- Patient Reference: _____
- Gender*: Male / Female
- Age : _____
- Smoker*:
- Yes -> Last cigarette: < 15min / <30 min / <45 min / <1H / < 2H / < 4H / > 4H
- No -> Never smoked
- Stopped < 1 month / < 6 months / < <1 yr. / < 5yrs / < 10 yrs / > 10 yrs
- Last alcoholic consumption*: < 1H / < 2H / < 4H / < 8H / > 8H / Never
- Currently having a flu*: Yes / No
- Stress level*: Low / Normal [nervous for measurement] / High
- Currently used medication:
- Currently following a diet:
- _____
- Known diseases:
- [A] Asthma
- [B] Bronchitis
- [C] Cancer
- [D] Cardiac problems
- [E] COPD
- [F] Diabetes
- [G] Metabolic Disease
- [H] Peptic Ulcer
- [I] Pneumonia
- [J] Rheumatism
- Other :
- Remarks
- Patient has Condition/Disease*: Yes / No

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