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FACULTY OF ENGINEERING

17 - 21 October 2016 at Michigan State University, Workshop on Future Directions in Fractional Calculus Research and Applications

How the fractional order impedance models influenced lung function device trends

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A historical perspective

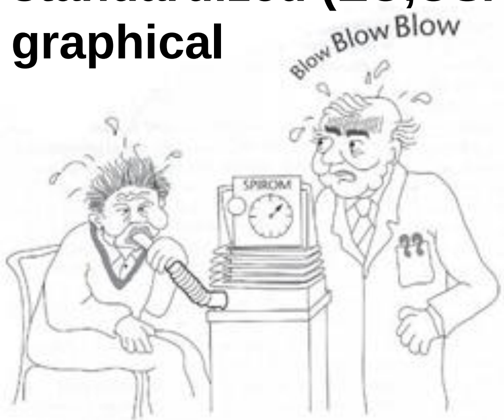
"If I have seen a little further it is by standing on the shoulders of giants"
Sir Isaac Newton

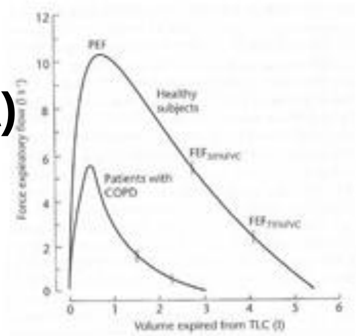
WHY THIS TEST?

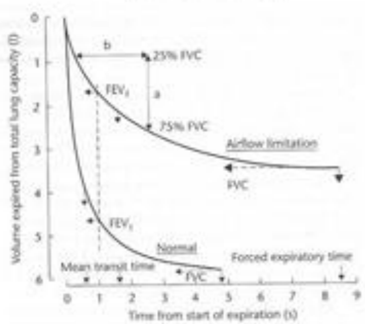
SPIROMETRY
BODY PLETHYSMOGRAPHY

- **Special manoeuvres**
- **Repetitive**
- **Fatigue**
- **Difficult to perform in elderly and children**

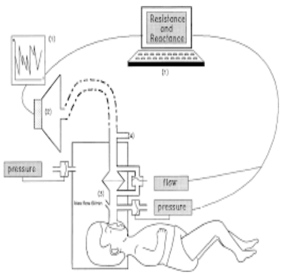
+ reference values
+ standardized (EU,USA)
+ graphical







FORCED OSCILLATION TECHNIQUE
+ no manoeuvres
+ short
+ graphical
+ classification
- not standardized
- limited reference values (4-48Hz)



1950
DuBois

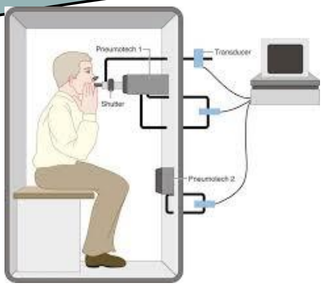
1970
Lutchen
Kaczka

1980
Bates
Maksym
Hantos
Stamenovic

1990
Suki
Desager
VandeWoestijne

2000
Oostveen

2003
DiMelo
Ionescu

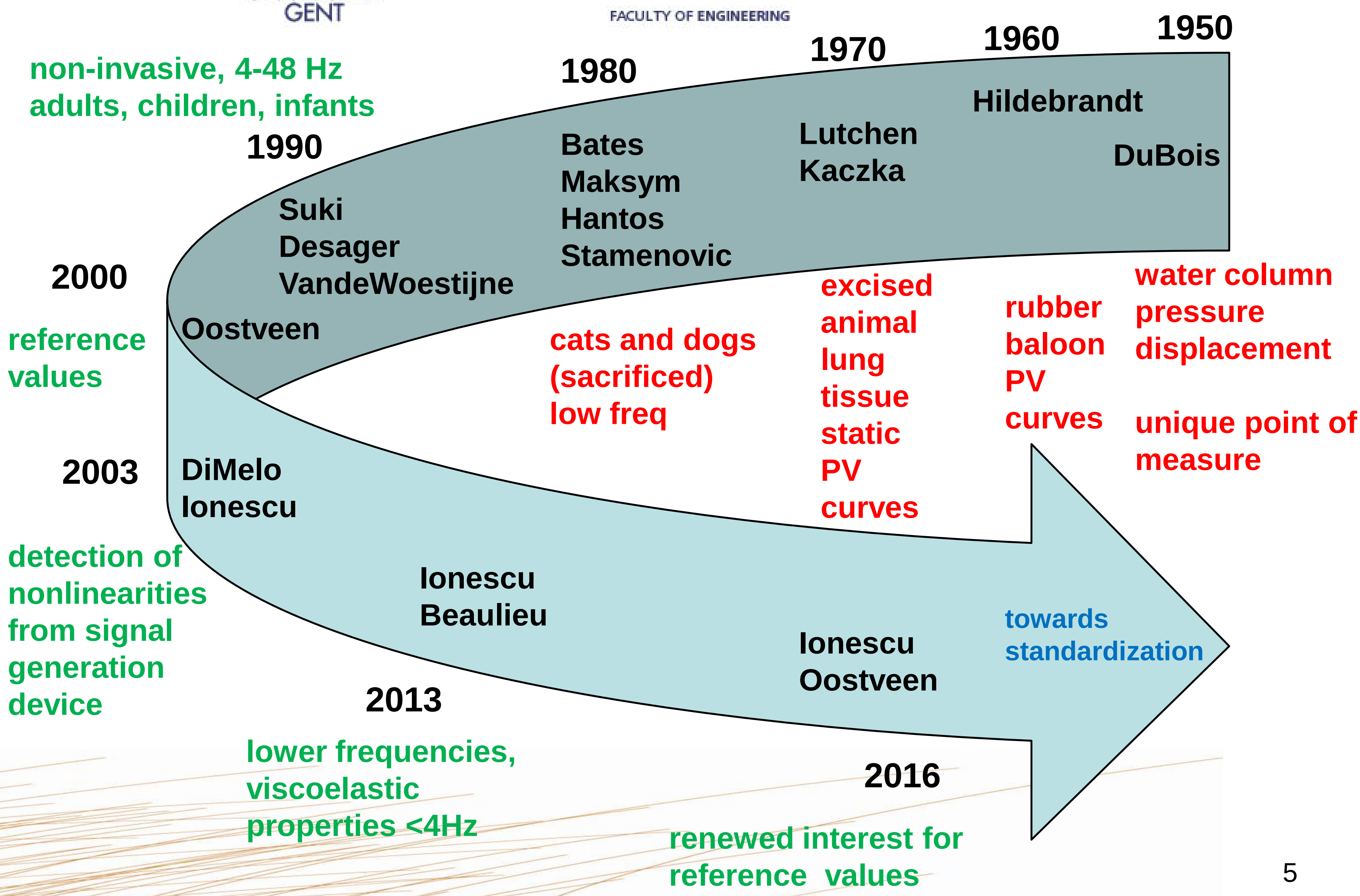


Ionescu
Beaulieu

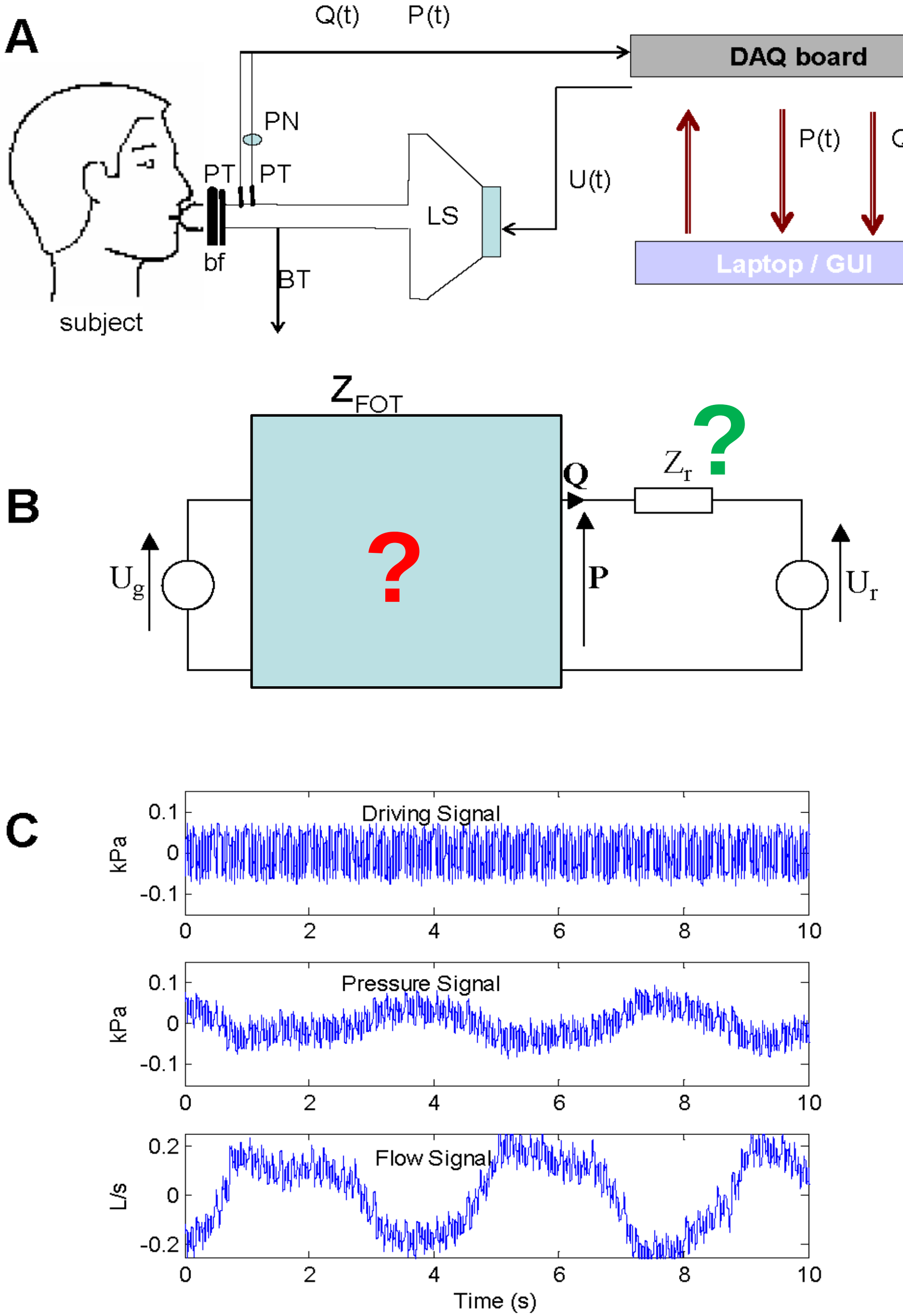
2013

Ionescu
Oostveen

2016


1950
1960
1970
1980
1990
2000
2003
2013
2016
non-invasive, 4-48 Hz
adults, children, infants
Hildebrandt
DuBois
Lutchen
Kaczka
Bates
Maksym
Hantos
Stamenovic
Suki
Desager
VandeWoestijne
Oostveen
water column
pressure
displacement
unique point of
measure
rubber
baloon
PV
curves
excised
animal
lung
tissue
static
PV
curves
cats and dogs
(sacrificed)
low freq
reference
values
DiMelo
Ionescu
detection of
nonlinearities
from signal
generation
device
Ionescu
Beaulieu
Ionescu
Oostveen
towards
standardization
lower frequencies,
viscoelastic
properties <4Hz
renewed interest for
reference values

THE PRINCIPLE



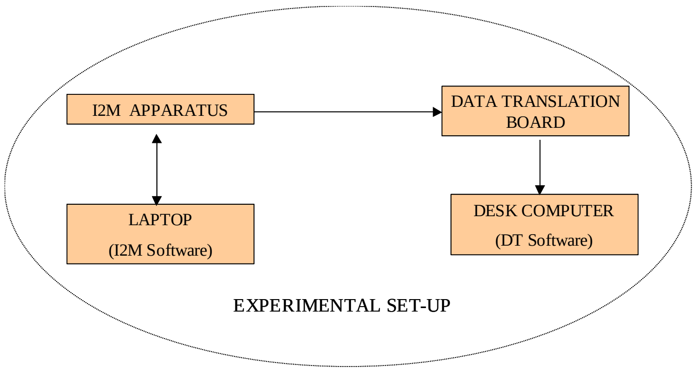
E. Oostveen, D. Macleod, H. Lorino, R. Farre´, Z. Hantos, K. Desager, F. Marchal, "The forced oscillation technique in clinical practice: methodology, recommendations and future developments", Eur Respir J, 22, 1026–1041, (2003)

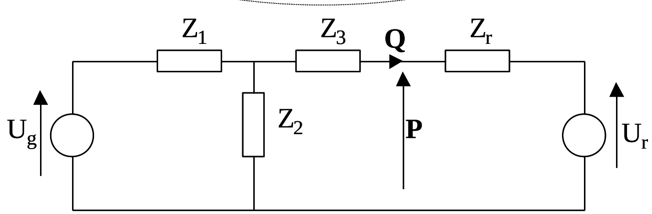
Parametric models

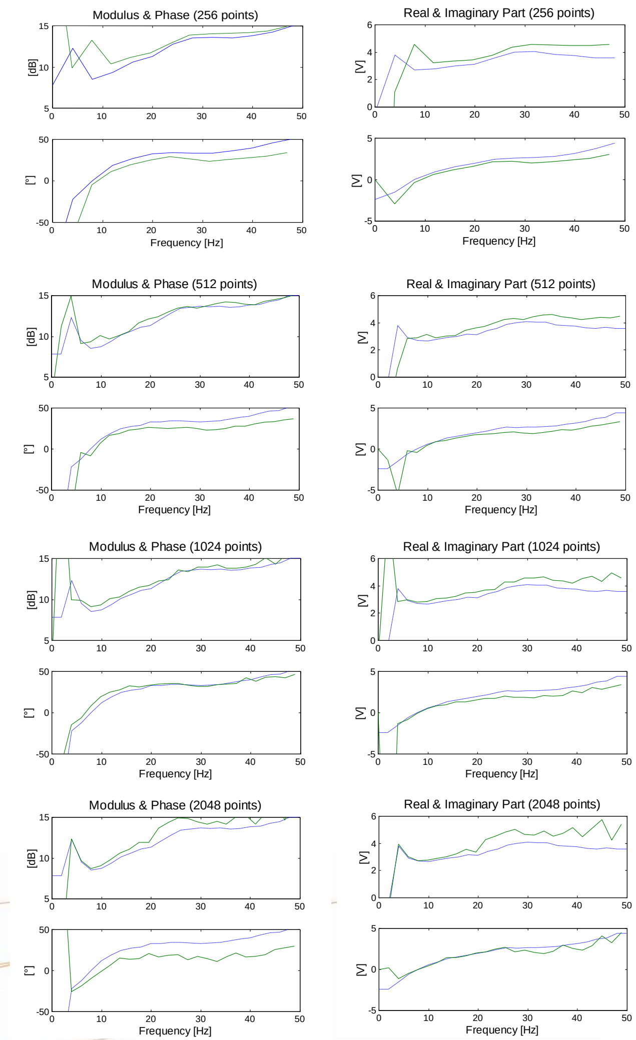
(integer and fractional orders)

2003: MEDIUM FREQS 4-48 Hz

- identification of the fractional order impedance model
-modelling the interaction with device (acts as a load for the lungs)
- observe breathing effect (bias at low freq)







FRACTIONAL ORDER IMPEDANCE PARAMETRIC MODEL WORKS WELL, BUT WHERE DO THE TERMS COME FROM?

$$Z(s) = R + Ls + \frac{1}{Cs^{\alpha}} = R + Ls + \frac{D}{s^{\alpha}}, \text{ with } 0 < \alpha \leq 1$$

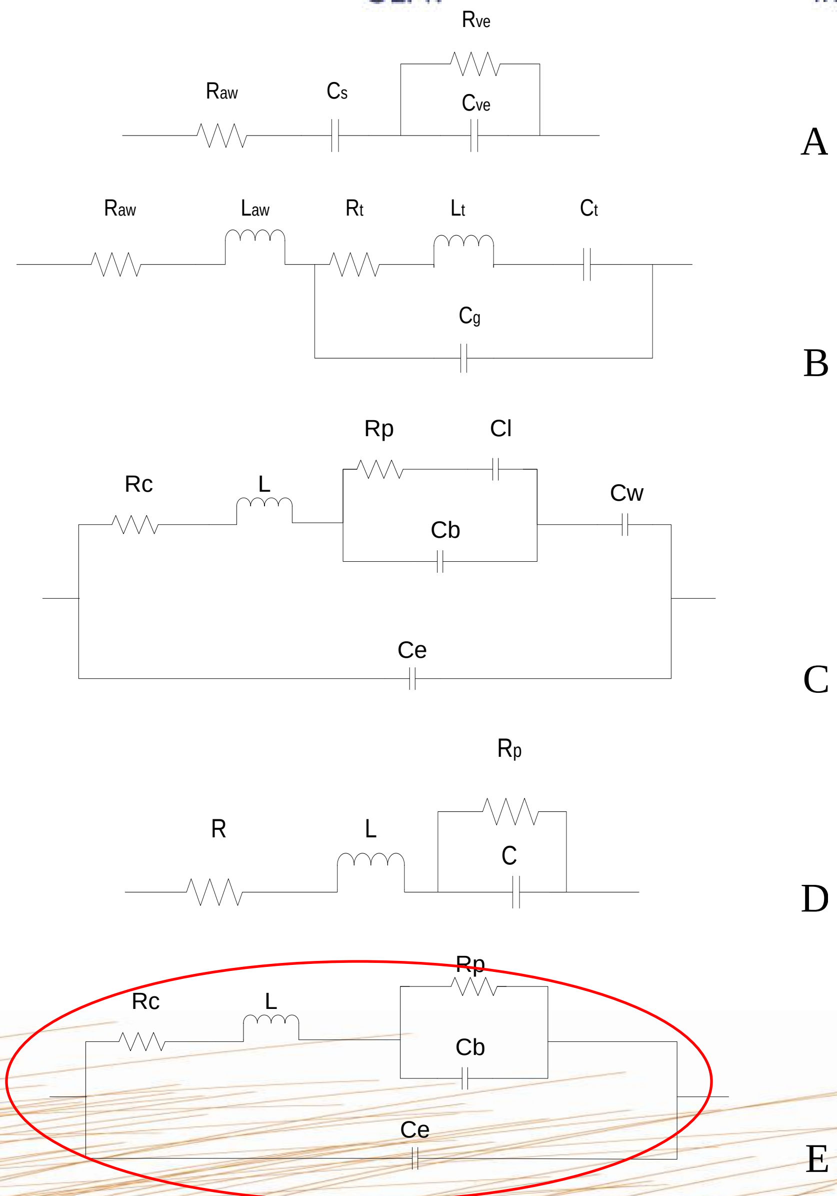
CP4 model

•Ionescu C.M., De Keyser R., "A Novel Parametric Model for the Human Respiratory System". In: Proceedings of the IASTED International Conference on Modelling and Simulation, USA, Acta Press, Anaheim, pp. 246-251, 2003

Example of real patient data given from company for evaluating the model

Frequency	Re1 Healthy	Im1 Healthy	Re2 Asthma	Im2 Asthma	Re3 COPD	Im3 COPD
4	2.623	-0.394	3.95	-1.75	0.1725	-0.1391
6	2.433	-0.109	3.65	-1.5	0.2047	-0.0956
8	2.421	0.136	3.3	-0.75	0.1841	-0.0742
10	2.417	0.266	3.25	-0.5	0.1699	-0.0693
12	2.467	0.427	3.1	-0.35	0.1546	-0.0609
14	2.396	0.512	2.98	-0.35	0.1440	-0.0500
16	2.36	0.671	2.8	-0.3	0.1399	-0.0358
18	2.43	0.766	2.7	-0.15	0.1365	-0.0138
20	2.417	0.812	2.6	0.10	0.1326	0.0027
22	2.465	1.011	2.65	0.5	0.1423	0.0157
24	2.515	1.213	2.58	0.6	0.1501	0.0256
26	2.398	1.357	2.55	0.7	0.1506	0.0332
28	2.491	1.394	2.53	0.75	0.1513	0.0339
30	2.643	1.62	2.3	1	0.1576	0.0386
32	2.589	1.534	2.4	1.45	0.1499	0.0470
34	2.646	2.043	2.45	1.52	0.1526	0.0487
36	2.694	1.849	2.55	1.7	0.1614	0.0532
38	2.584	2.111	2.35	2.3	0.1603	0.0642
40	2.772	2.135	2.4	2.35	0.1647	0.0751
42	2.586	2.476	2.5	2.5	0.1702	0.0855
44	2.908	2.395	2.53	2.65	0.1757	0.0960
46	3.083	2.537	2.48	2.7	0.1797	0.0966
48	2.894	2.608	2.49	3.1	0.1885	0.1002

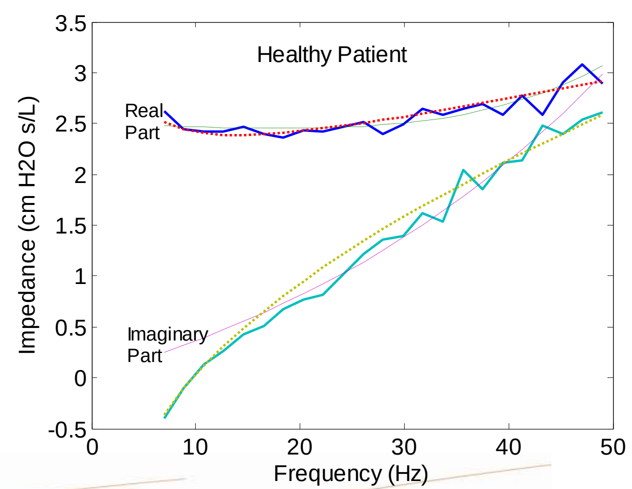
2005-2007: parametric identification of impedance



Comparison to other models established in literature

Results in conclusion that fractional order impedance has minimum nr parameters with best fitting results

Model structures according to their electrical analogies, given as: (A) the viscoelastic model; (B) the DuBois model; (C) the Mead model; (D) the extended RLC and (E) the RLCES model.

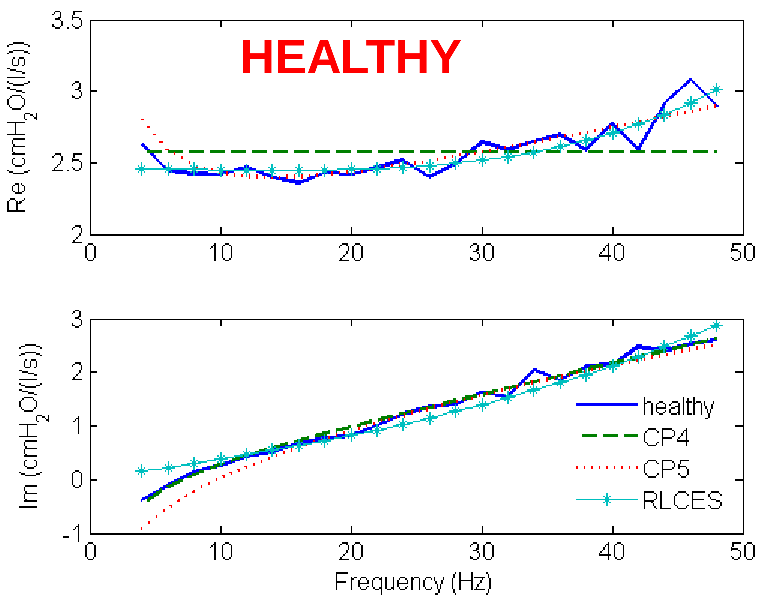


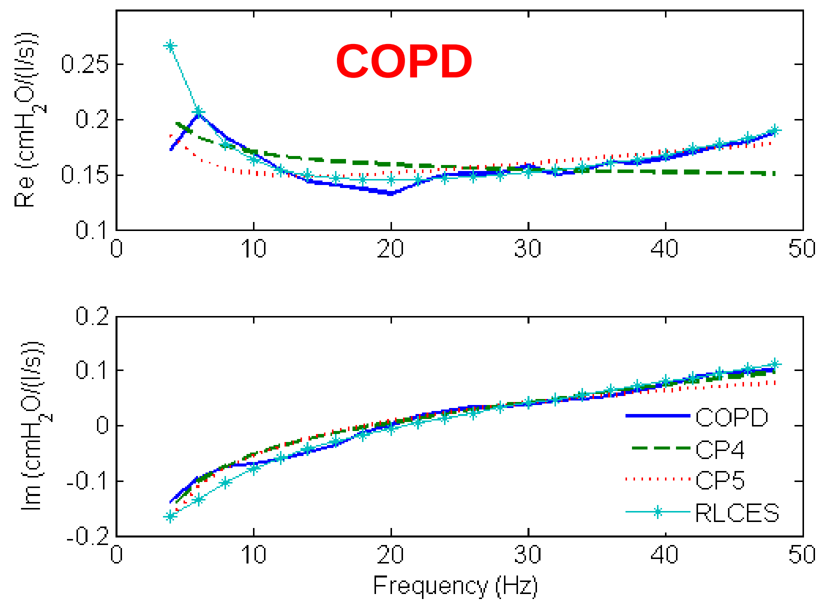
RLCES model offered good trade off between accuracy and complexity

Ionescu C-M, De Keyser R. Parametric models for characterizing respiratory input impedance. Journal of Medical Engineering & Technology. 2008;32(4):315–24

Exploring the problems

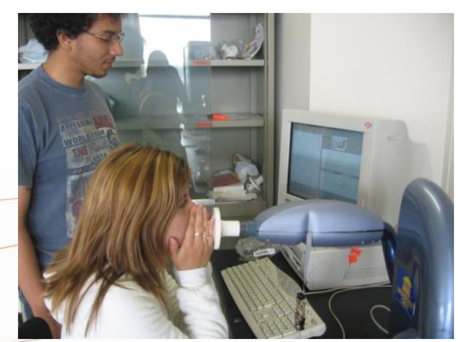
First resonance after breathing frequency
Classification between healthy and respiratory disorders
Requires TWO fractional order terms in impedance model





CP4 model fails

RLCES and CP5 - OK



Lower frequencies seem markedly changed with disease

Viscoelastic properties

Are airway structural changes correlated with tissue properties?

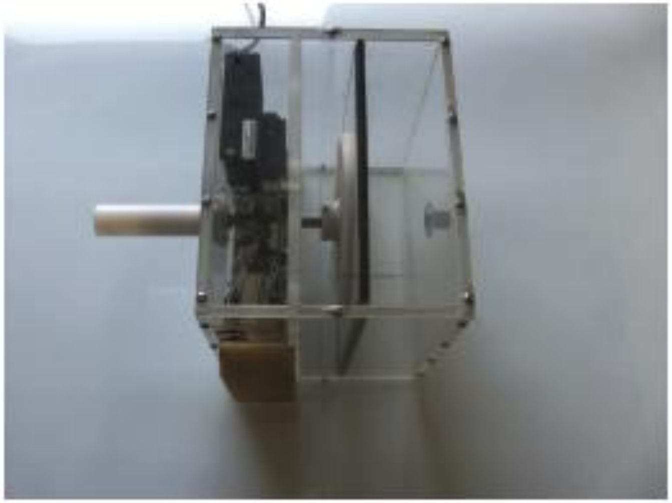
Closer to breathing – interference

2005 -… nonlinearities

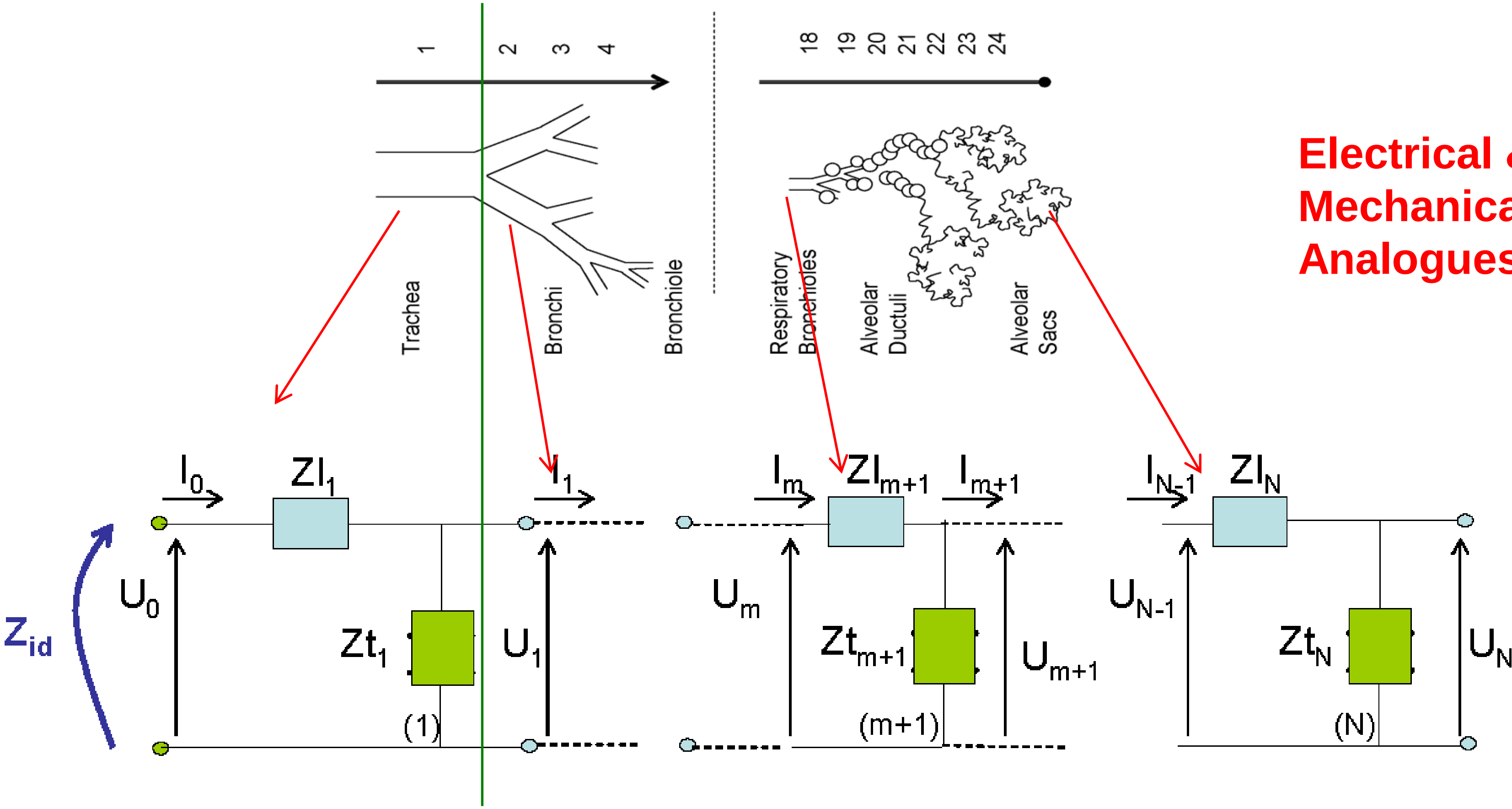
Signals applied to the patient with frequencies closer to the breathing frequency exhibit nonlinear phenomena (e.g. AM)

Idea: detect, possibly extract these effects and explore them as a diagnosis tool

Results: a series of alternate methods to extract impedance data from pressure and/or flow measurements in parallel with efforts to change the device for applying other frequencies than the standard 4-48Hz



Where do the model parameters come from?



Electrical & Mechanical Analogues

C.M. Ionescu, P. Segers, R. De Keyser, "Mechanical properties of the respiratory system derived from morphologic insight", IEEE Trans Biomed Eng, 56(4), 949– 959, (2009)

C.M. Ionescu, I. Muntean, J.T. Machado, R. De Keyser, M. Abrudean, "A theoretical study on modelling the respiratory tract with ladder networks by means of intrinsic fractal geometry", IEEE Trans Biomed Eng, 57(2), 246–253, (2010).

Morphology, structure and functionality combined led to appearance of fractional order impedance forms

Electrical analogy

Fractional order related to pseudo-recurrence in the airways props

Alterations in airway properties led to changes in fractional order values

Mimic disease structural changes and remodelling effects

Ionescu C-M. The human respiratory system : an analysis of the interplay between anatomy, structure, breathing and fractal dynamics, Springer, Series in Bio-Engineering 2013

2009-2011: time domain

Pressure-Volume curves
Impulse Responses
Classification Methods (fractal dimension, dendograms)

Ionescu C-M. The human respiratory system : an analysis of the interplay between anatomy, structure, breathing and fractal dynamics, Springer, Series in Bio-Engineering 2013

Minimal clinical interest due to lack of mathematical relation from time domain to structural changes

Ionescu C., De Keyser R., "Time domain validation of a fractional order model for human respiratory system", in the 14th IEEE Mediterranean Electrochemical Conf (MELECON08),Ajaccio, Corsica, IEEE Cat Nr CFP08MEL-CDR, ISBN 978-1-4244-1633-2, pp. 89-95, 2008

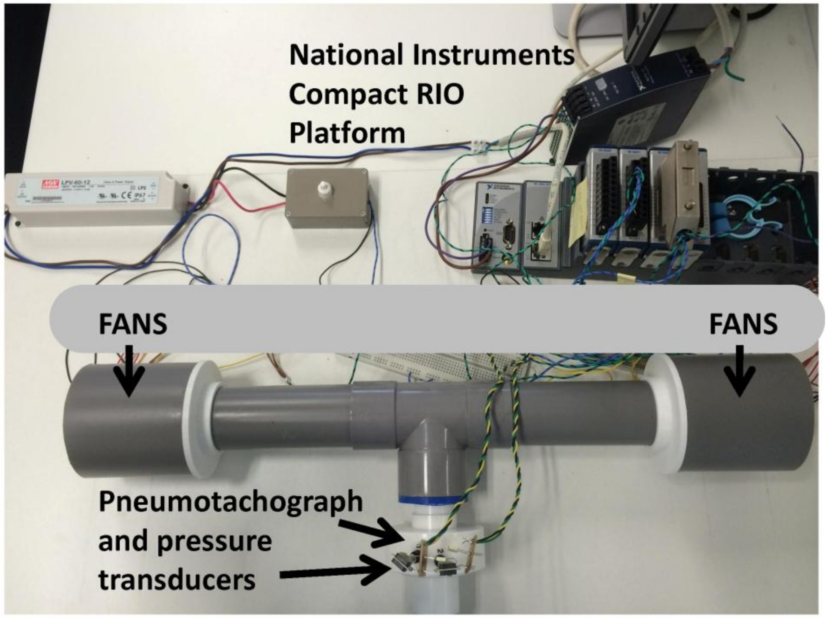
Ionescu C.M, J.Tenreiro Machado, R. De Keyser, Is multidimensional scaling suitable for mapping the input respiratory impedance in subjects and patients?, Computer Methods and Programs in Biomedicine, 104(3), E189-E200, ISSN 0169-2607, 2011

Ionescu C., Machado J.T., De Keyser R., "Analysis of the Respiratory Dynamics During Normal Breathing by Means of Pseudo-phase Plots and Pressure–Volume Loops", *IEEE Transactions on Systems, Man & Cybernetics, Part A: Systems*, DOI: 10.1109/TSMCA.2012.2187888, 43(1), 53-62, 2013

Nigmatullin R. Ionescu C, Baleanu D., "NIMRAD: novel technique for respiratory data treatment", J of Signal Image and Video Processing, 8(8), 1517-1532, 2014

Evolution of low-frequent oscillations device generations 1, 2, 3,…

2013: NEW GENERATION DEVICE for low frequencies



DETECT NONLINEAR EFFECTS IN INSTRUMENTATION

CORRECT THE IMPEDANCE DATA

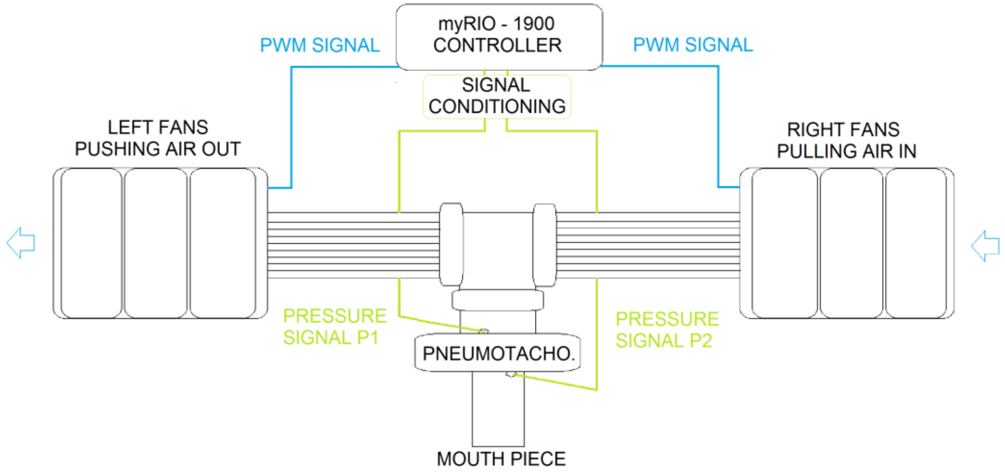
EVALUATE IN COPD PATIENTS (SMALL AIRWAYS)

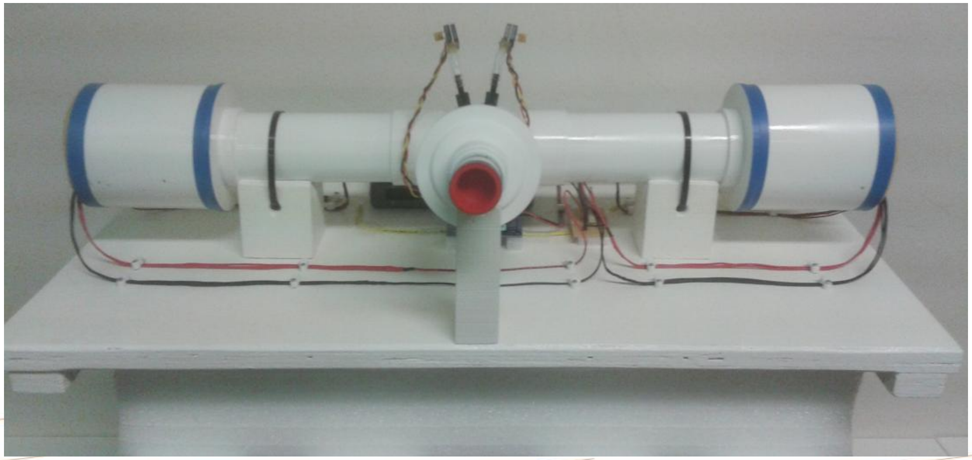
Ionescu C., De Keyser R., Sabatier J., Oustaloup A., Levron F., "Low frequency constant-phase behavior in the respiratory impedance", *Biomedical Signal Processing and Control*, 6, 197-208, 2011

Ionescu C.M., G. Vandersteen, J. Schoukens, K. Desager, R. De Keyser, "Measuring Nonlinear Effects in RespiratoryMechanics: A Proof of Concept for Prototype Device and Method", IEEE Transactions on Measurement and Instrumentation, 63(1), 124-134, 2014

Maes H., Vandersteen G, Muehlebach M., Ionescu C.M., "A ventilator based, low frequent, forced oscillation technique apparatus", IEEE Transactions on Measurement and Instrumentation, 63(3), 603-611, 2014

NEXT GENERATION





Uses feedforward and feedback control compensation of breathing effects

Longer measurement time

Non-invasive

Patient-friendly

Oscar Olarte, Robin De Keyser, Clara M. Ionescu, "Fan-based device for non-invasive measurement of respiratory impedance: Identification, calibration and analysis", *Biomedical Signal Processing and Control,* vol 30, 127-133, 2016

2013-2016: mathematical models of viscoelasticity

Structural changes with disease modelled and identified in impedance data at frequencies below 2 Hz (unpublished work)

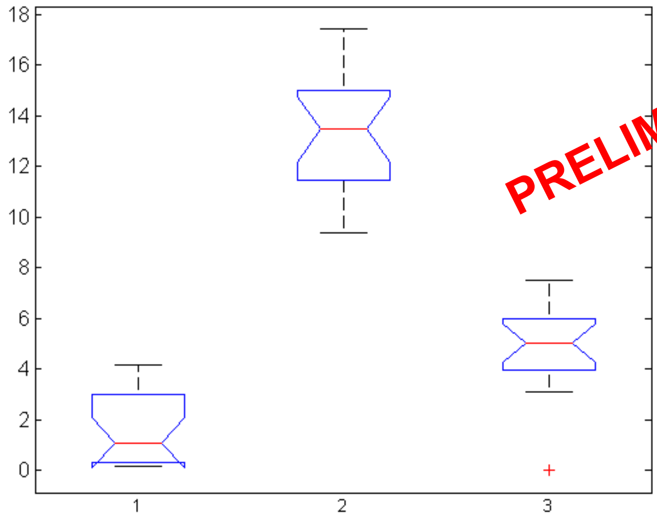
Initial results indicate the potential of fractional order impedance models to explain these changes (unpublished work)

Lack of large population database
Statistics not reliable to extract (yet) reference values

VISCOELASTIC PROPERTIES

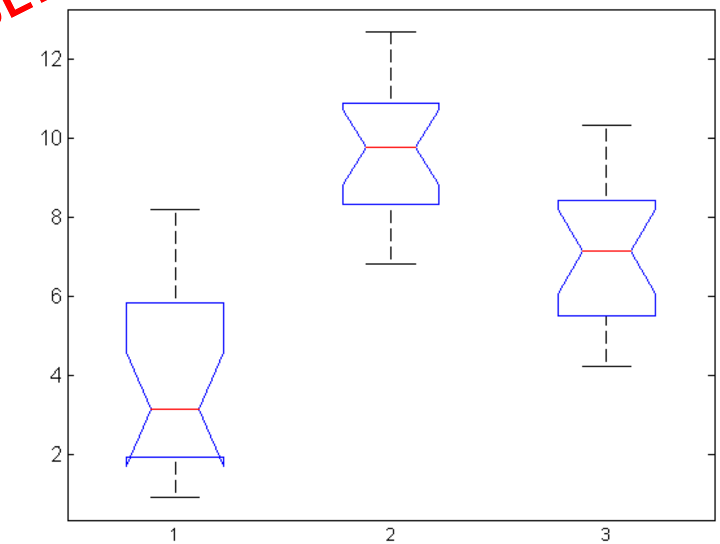
PRELIMINARY RESULTS !

Tissue Damping G



Healthy COPD II COPD III

Tissue Elastance H

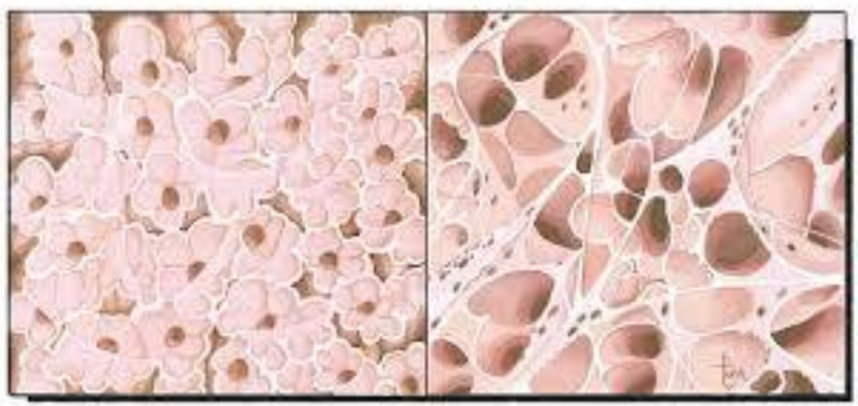


Healthy COPD II COPD III

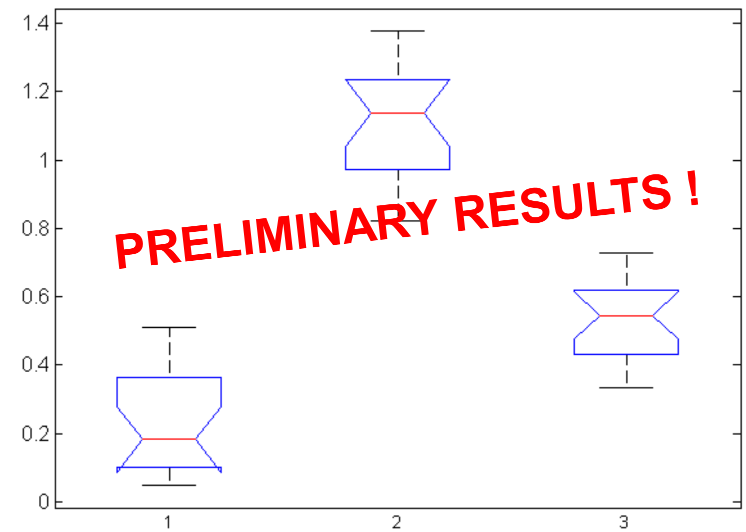
Damping increases in COPD due to fibrotic tissue (+stiffness)
Elastance increases in COPD due to broken alveolar spaces

CHANGES IN TISSUE STRUCTURE

Tissue heterogeneity



A Normal Lung B Emphysema



Healthy COPD II COPD III

From our model structure we now understand that in healthy, the alveolar impedances are (more) homogeneous compared to COPD

Clinical insight: **COPD II has more varied changes in alveolar structure than in COPD III when disease has progressed and changes are more pronounced and more specific. This explains higher heterogeneity in COPD II than in COPD III.**

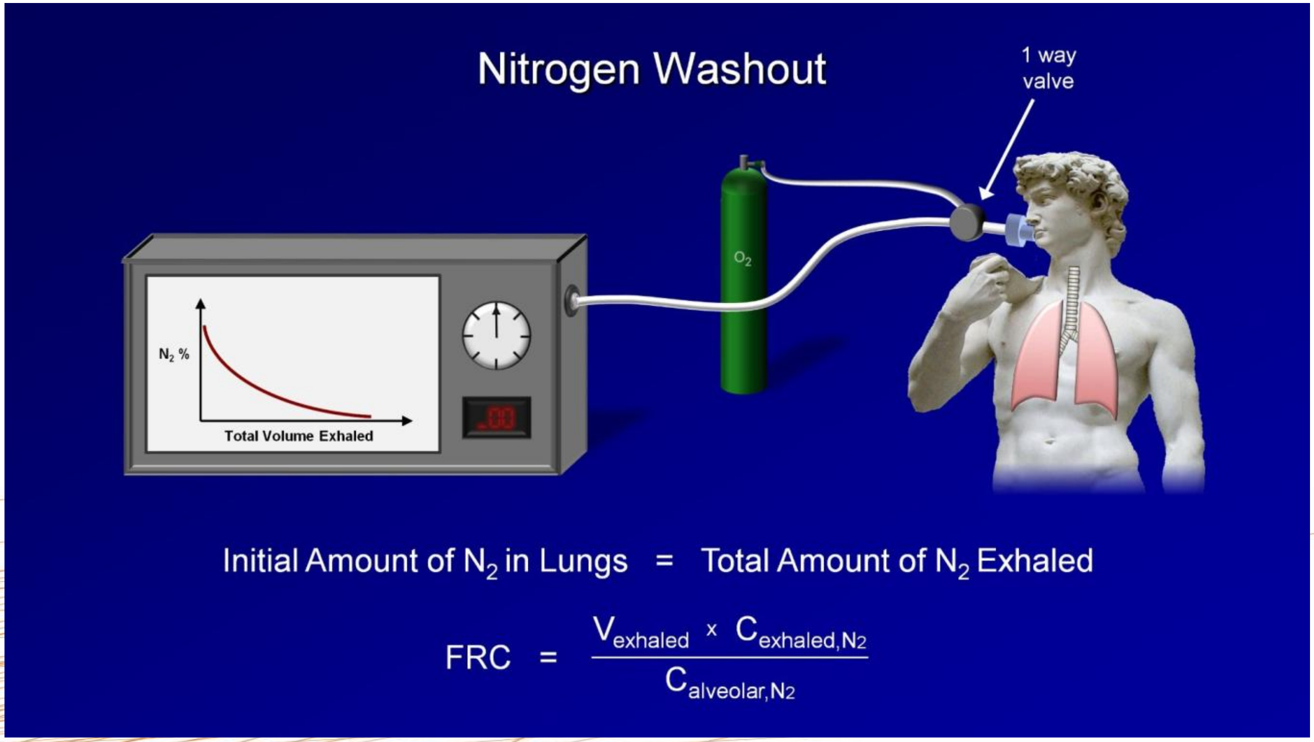
A higher ground implies new perspectives

After 2016…..

Characterize DIFFUSION is the next step – link to HETEROGENEITY
Move away from macro- to micro-scale analysis of structural changes

COPD, aka *small airway disease* → need to look into the details

How to test diffusion? Standardized wash-out test



WHAT WE HAVE ACHIEVED IN THE PAST DECADE

- ✓ **Fractional order impedance parameters have morphological meaning**
- ✓ **Identified values are physiologically meaningful**
- ✓ **Mathematical platform to study viscoelastic properties as a function of disease progression**
- ✓ **Data of impedance at frequencies close to breathing**
- ✓ **Data of nonlinear contributions as a function of disease presence and evolution**
- ✓ **Device development to compact, easy-to-transport and patient-friendly form**

OPEN POINTS OF INTEREST

COLLABORATION OPEN FOR:

- **wash out clinical tests and correlation to impedance data, new model**
- **reference values in multi-centre (international) 0.1 – 1.7 Hz**
- **how to obtain efficient time domain impulse response models from limited-time measurement data**

IFAC World Congress 9-14 July 2017, Toulouse, France

Open Invited Track on

Control and Data Driven Modelling in Biomedicine
https://www.ifac2017.org/OIT#bda14

6-page full paper submission deadline 31 october 2016,
use code: bda14

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We have come so far because of those who came before us