Signal Processing in Maternal-Fetal Medicine

V. John Mathews
Dept. Electrical & Computer Engineering
University of Utah
Salt Lake City, UT 84112

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Preamble, Disclaimers, etc.

- I am not an expert in maternal-fetal medicine
- I know a little bit of signal processing
- I work with a few doctors who truly believe in merging engineering with medicine and creating model-based diagnostic techniques
- What I will talk about is about some of the tools that have been built in recent years to facilitate the development of engineering models in predicting maternal-fetal diseases
- The signal processing techniques we use are often very simple, but they do make a difference

Collaborators that Contributed to Creating this Presentation

- Piet Struijk, Erasmus University, Rotterdam
- Lanka Fernando, PhD from University of Utah
- Mike Varner, Maternal-Fetal Medicine, U. Utah
- Ed Clark, Pediatrics, U. Utah
- Juriy Wladimirroff, Erasmus University, Rotterdam
- Eric Steegers, Erasmus University, Rotterdam

- A lot of the material for this talk came from the PhD theses written by Lanka Fernando and Piet Struijk

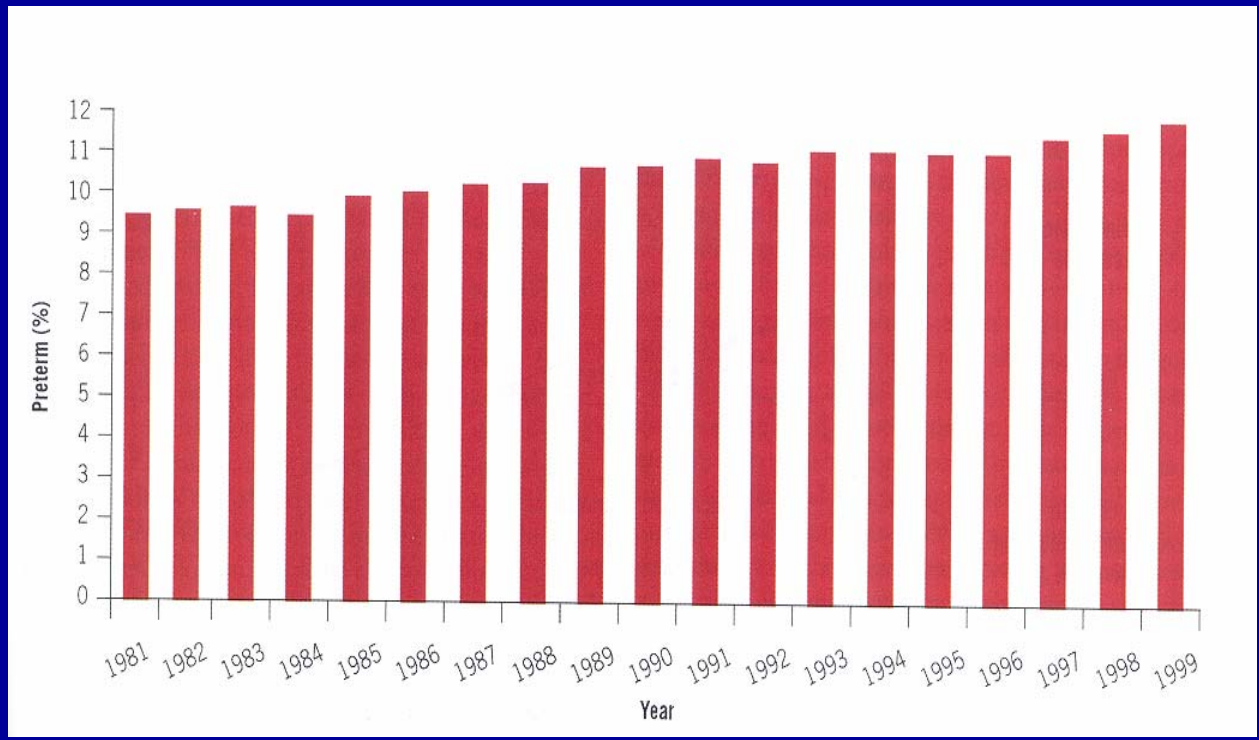
Motivation

- The last century saw dramatic reductions in maternal, fetal and newborn morbidity and mortality
  - 90% reduction in infant mortality
  - Significant increase in life expectancy of newborns
- In spite of this
  - Eight out of 1000 newborn infants have some form of heart defect
  - Pre-eclampsia complicates 6-8% of all pregnancies
  - Approximately 12% of the pregnancies result in premature deliveries (Gestational age < 36 weeks)
  - 3-10% suffer from fetal growth restrictions

To put this in perspective …

- In an average week in the United States
  - 78,058 babies are born
  - 8,985 babies are born preterm
  - 538 babies will die before their first birthday
- Preeclampsia represents an annual health care cost in excess of $7 billion in the US
- There is evidence indicating that small for gestational age children are at risk for early onset of adult cardiovascular diseases.
- Cost of treating heart diseases and lost productivity due to such diseases in 2001: $287 billion

Incidence of Preterm Deliveries in the USA



- 30% increase since 1981

Some other disturbing trends

- Childhood asthma incidences have more than doubled in recent decades
- Neurodevelopmental disorders affect 5-10% of 4 million babies born in the USA
- Significant increases in Leukemia and brain cancer over the last thirty years

National Children's Study

- Children's Health Act 2000
- Established the National Children's Study
- Follow 100,000 children from conception through 21 years of age to understand the children's development and the effect of various environmental and other factors on their development
- Price tag - $2.7 billion over 25+ years
  - If this study facilitates the reduction of even 1% of early childhood and subsequent adult diseases, the savings in medical care expenses will pay for this study and more
  - Will the Congress follow through with the necessary funding?

Our goal

- Characterize the development of the normal fetus (and normal pregnancy) by tracking the evolution of various properties of measurable signals over the course of gestation
- Variations from the normal characteristics may mean abnormalities in the fetus or mother or both
- Develop appropriate tests to predict the likelihood of disease, hopefully much earlier than when symptoms of the disease appear
- Such tests will allow the caregivers to identify potential problem pregnancies, provide the additional attention as necessary and possibly initiate therapy

Doppler Ultrasound – Our Choice for Early Studies

- Non-invasive, no known safety issues
- Ultrasound exams are already part of standard prenatal care
- Can be administered as early as the 8th week of gestation
- Measurement of the blood flow in fetal arteries provide information about the fetal circulation system

So far …

- We have characterized the evolution of
  - Heart rate variability and associated parameters
  - Blood pressure in fetal aorta
  - Shear stress at fetal arterial walls
  - Coherence between maternal and fetal blood flows
- Tests for detecting/predicting
  - Certain congenital heart defects
  - Growth restricted pregnancies
  - Preeclampsia

  with some preliminary test results
- We have also developed some proteomics-based markers for preeclampsia

Measurement of Heart Rate Variability and Associated Factors

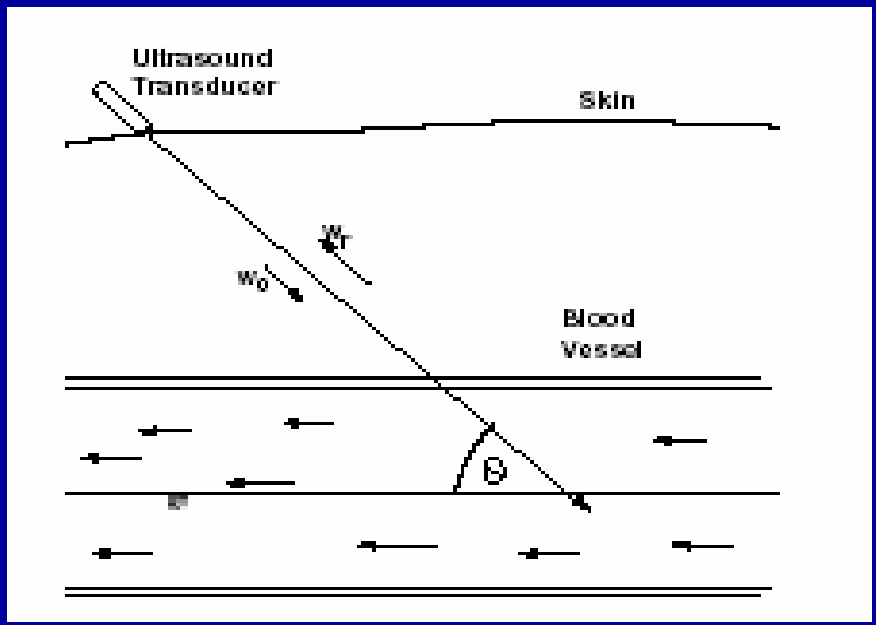
Nervous System Activity in Fetuses

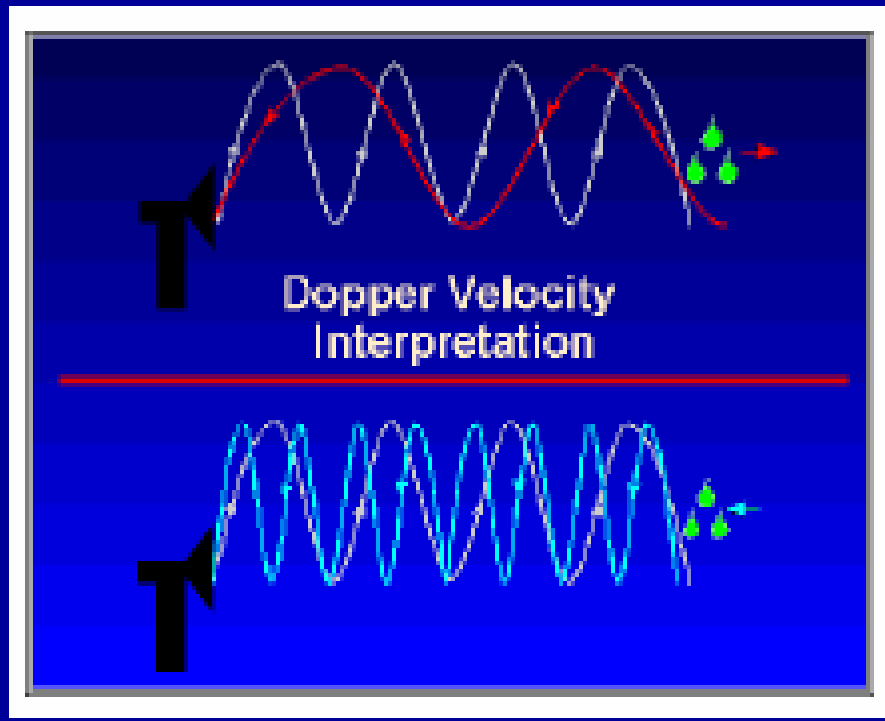
- Myofibrils in the cardiac muscles are responsible for the contractility of the myocardium
- By 8-10 weeks of fetal life, myofibrils appear in large numbers, increasing the efficiency of myocardial contractility and decreasing the heart rate
- The autonomic nervous system (consisting of parasympathetic nerves and sympathetic nerves) innervates cardiac muscles.
- Parasympathetic nerves develop first (maturing around 15 weeks). They also tend to reduce the heart rate. Sympathetic nerves takes till up to 30 weeks to mature.

Evolution of Heart Rate and HRV with Gestatational Age

- In a normally developing fetus, one would expect the heart rate to decrease till about 15 weeks of gestation
- HRV should stay approximately the same during this period.
- As other oscillatory mechanisms in the body (for example, the respiratory system) begin to develop, they affect the heart rate variability, and we expect the HRV to increase after the 15^{th} week of gestation.

A One-Slide Intro to Doppler Ultrasound





$$\omega_d = \frac{2v}{c}\omega_0 \cos(\theta)$$

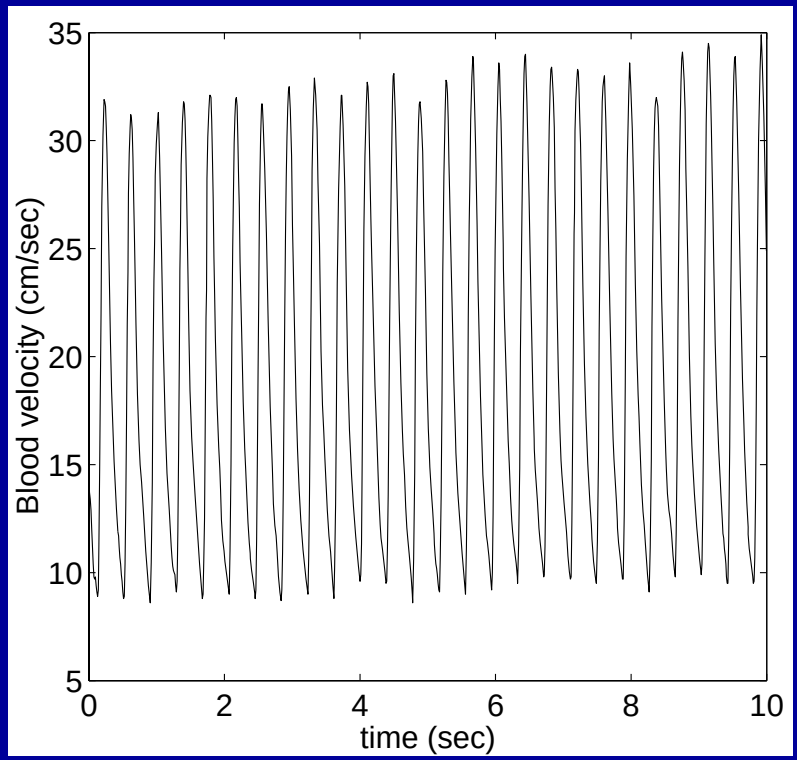
Approach to Measuring Heart Rate Variability

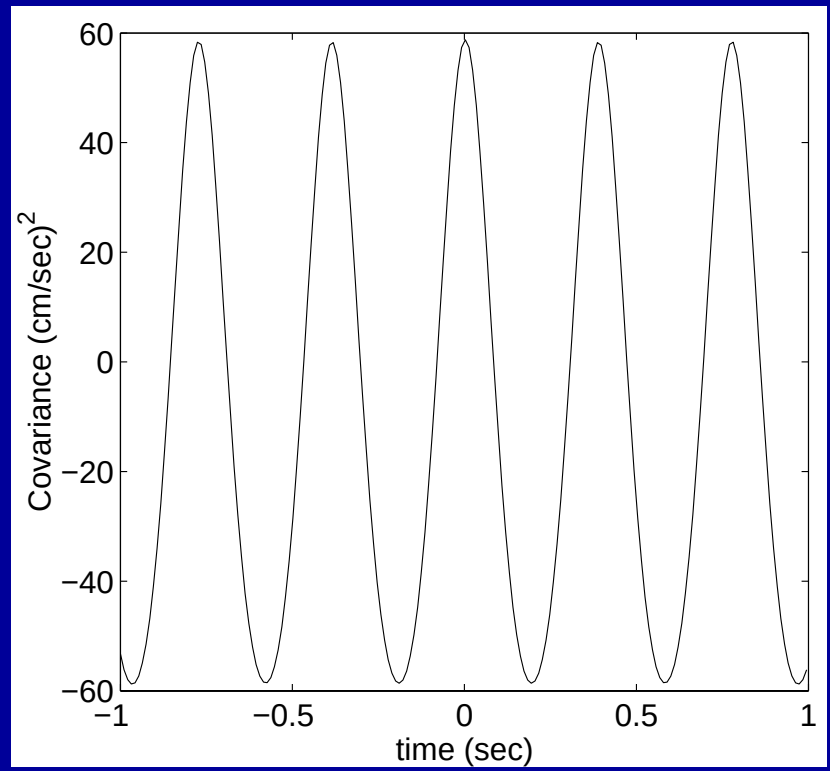
- Measure the blood flow velocity from a fetal artery using Doppler ultrasound
- Measure the frequency (heart rate) of the signal over small intervals of time
- Using an appropriate measure characterize the temporal variations in the heart rate over the course of the measurement

Fundamental Problem with the State-of-the-Art in Ultrasound-Based HRV Measurement

- Changes in the angle of insonation causes the velocity measurements to change.
- This causes currently available variability measures to change.
- Variations in the ambient noise levels from measurement to measurement changes the variability measures
- We would like to develop a method that is immune to the above problem

A Typical Fetal Blood Velocity Waveform





- The signal has narrowband characetristics.

Robust Measurement of HRV

- Divide the blood velocity waveform into small segments of length corresponding to a few heartbeats.
- In all our work, the segments contained no more than three heartbeats.
- Model the velocity waveform in each segment as a single sine wave corrupted by noise.
- Use MUSIC or a similar method to estimate the frequency and noise variance.
- It can be shown that the resulting frequency estimate is approximately the power-weighted mean frequency of the signal.

Angle-Independent Measurement of HRV

- Mean square error in the estimation of frequency is inversely proportional to the square root of the SNR
- Consequently, the variance of $\hat{f}_i(SNR_i)^{0.25}$ will be independent of the SNR, and in turn will not depend on the ambient noise level and the angle of insonation
- This method is specific to frequency estimation using MUSIC

Robust Measurement of HRV using Doppler Ultrasound

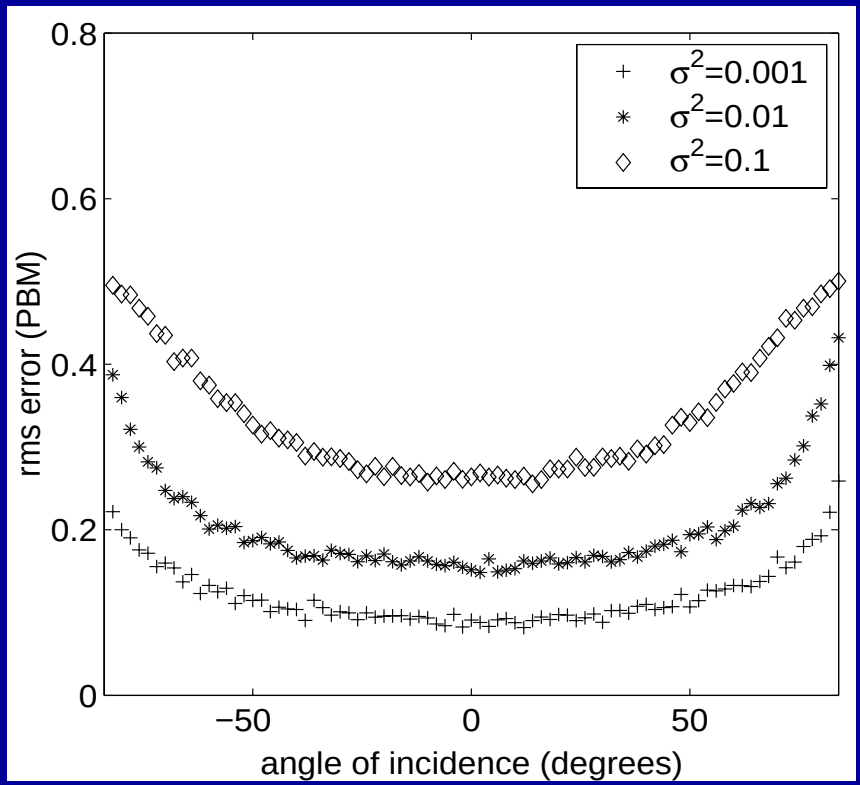
- Compute the average of the frequency estimate over all segments

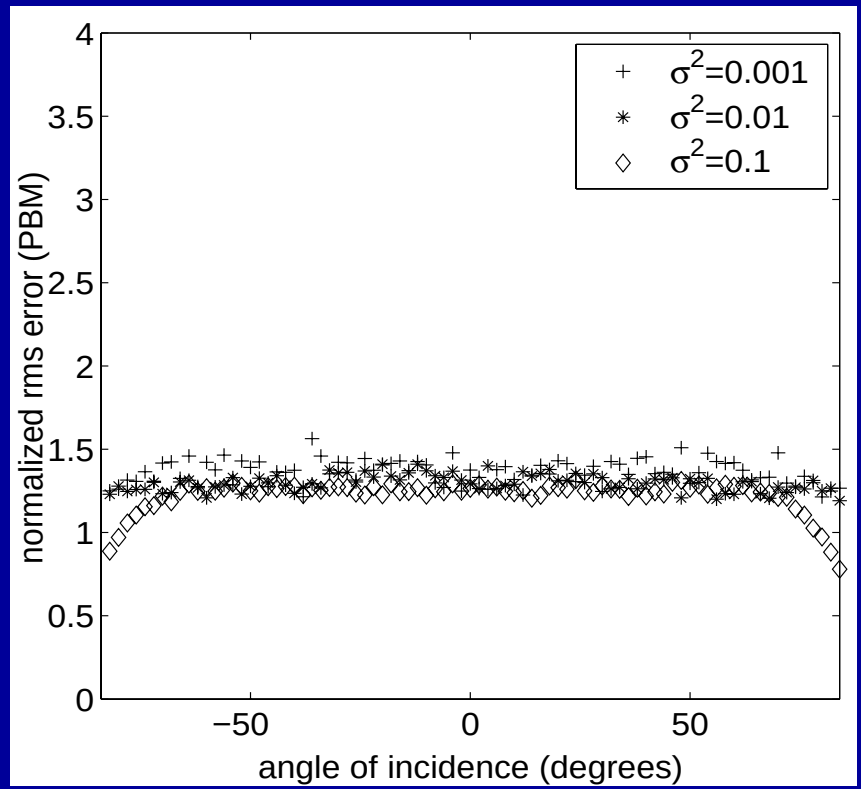
$$\overline{f} = \frac{1}{N}\sum_{i=1}^{N} \hat{f}_i$$

- Evaluate the normalized heart rate variability measure as

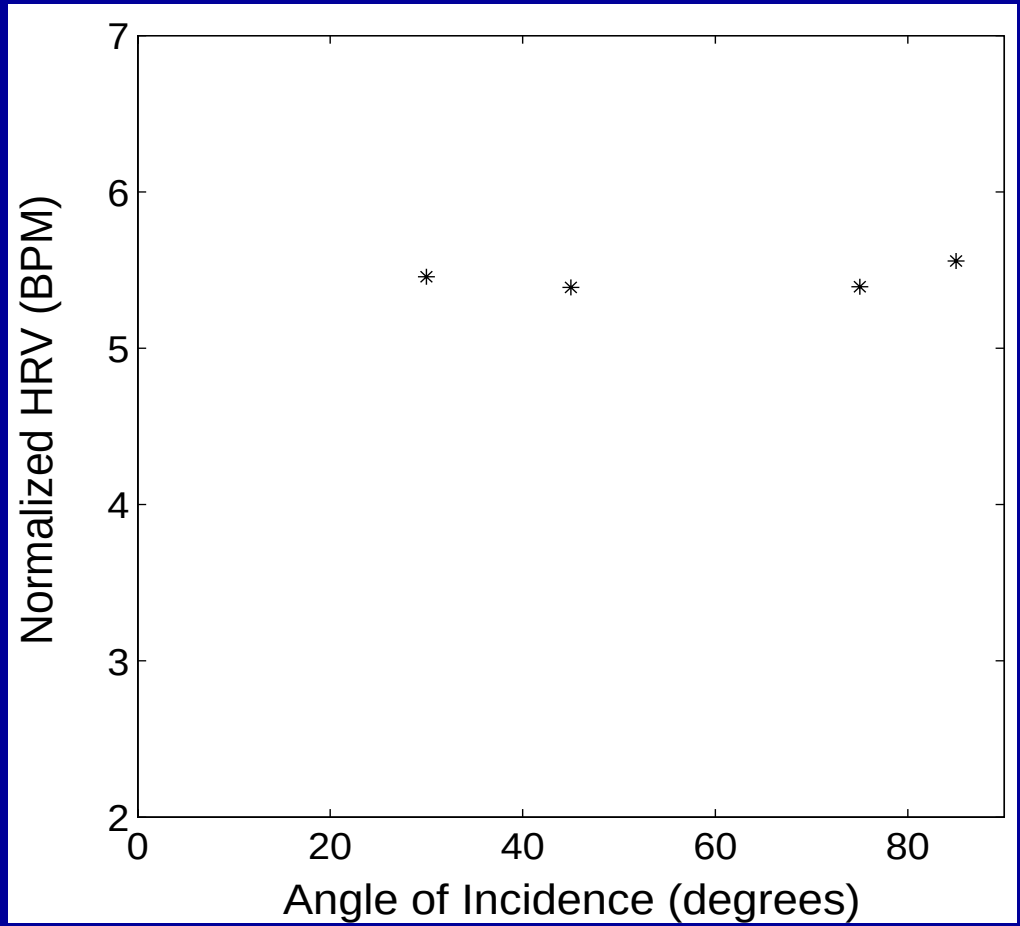
$$NHRV = \sqrt{\frac{1}{N}\sum_{i=1}^{N} (\hat{f}_i - \overline{f})^2 (SNR_i)^{0.5}}$$

Robustness of Normalized HLH Measure to Angle of Insonance and Ambient Noise Level

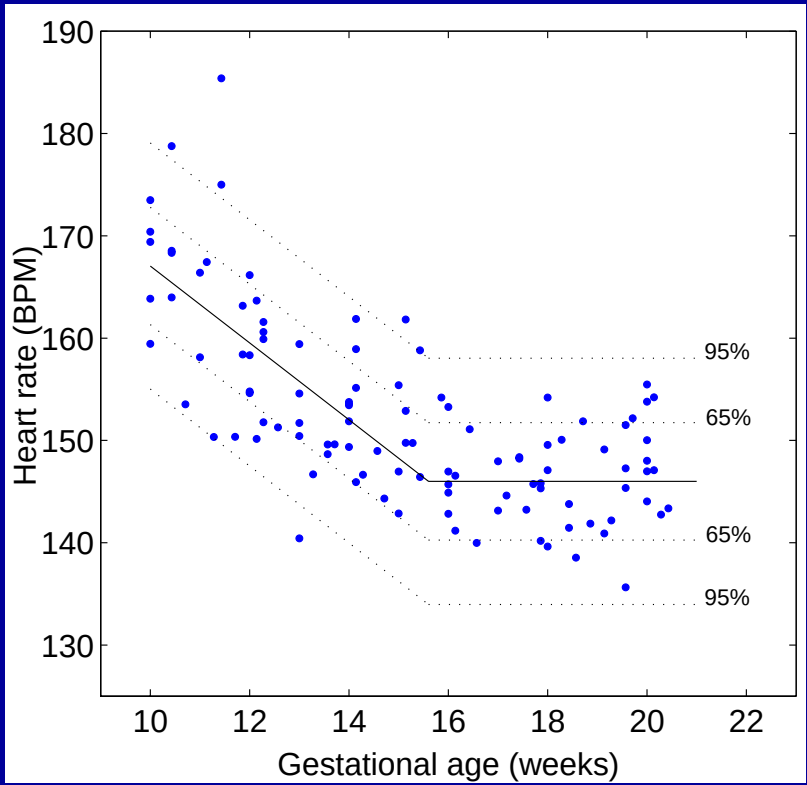


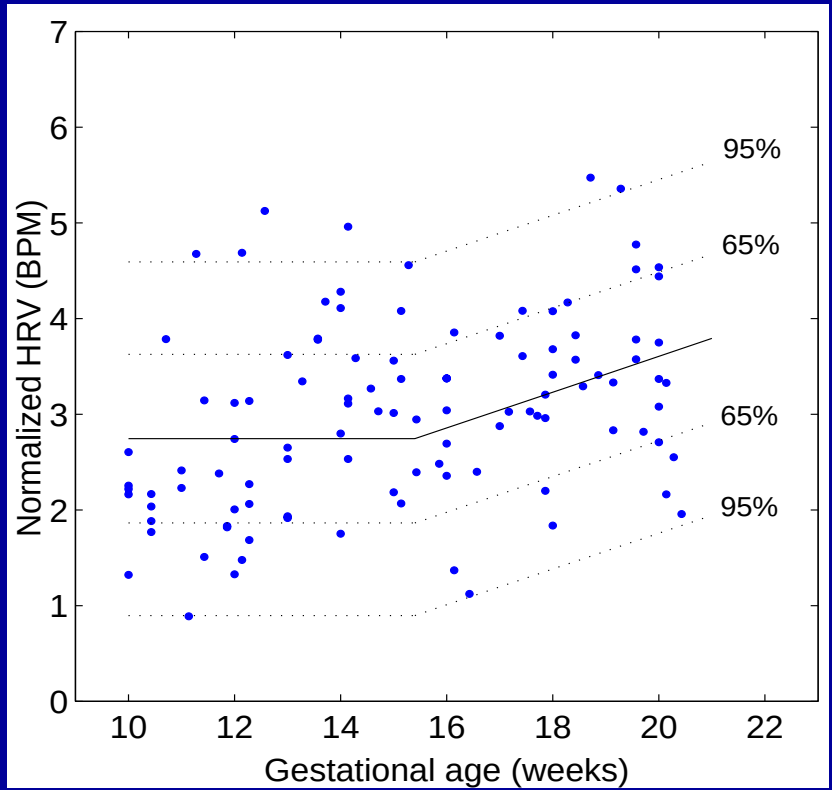


NHRV Measurements from a Human Artery

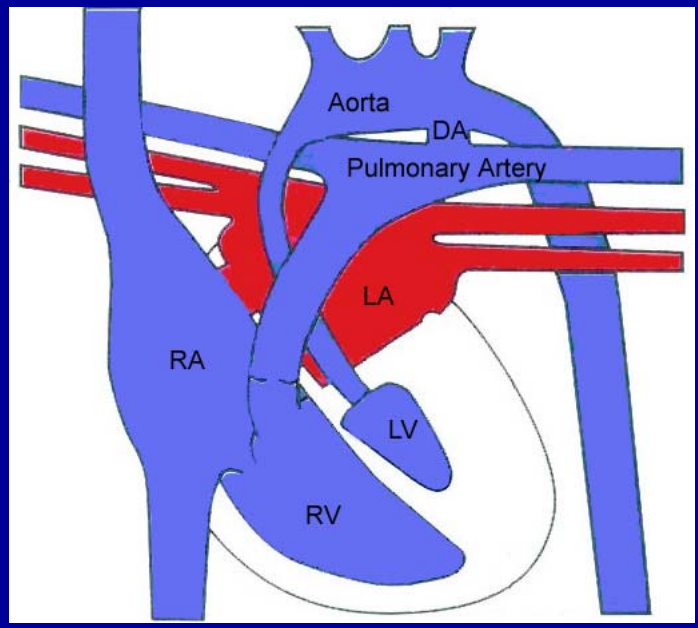


Use of Heart Rate Variability for Monitoring Fetal Cardiovascular Development



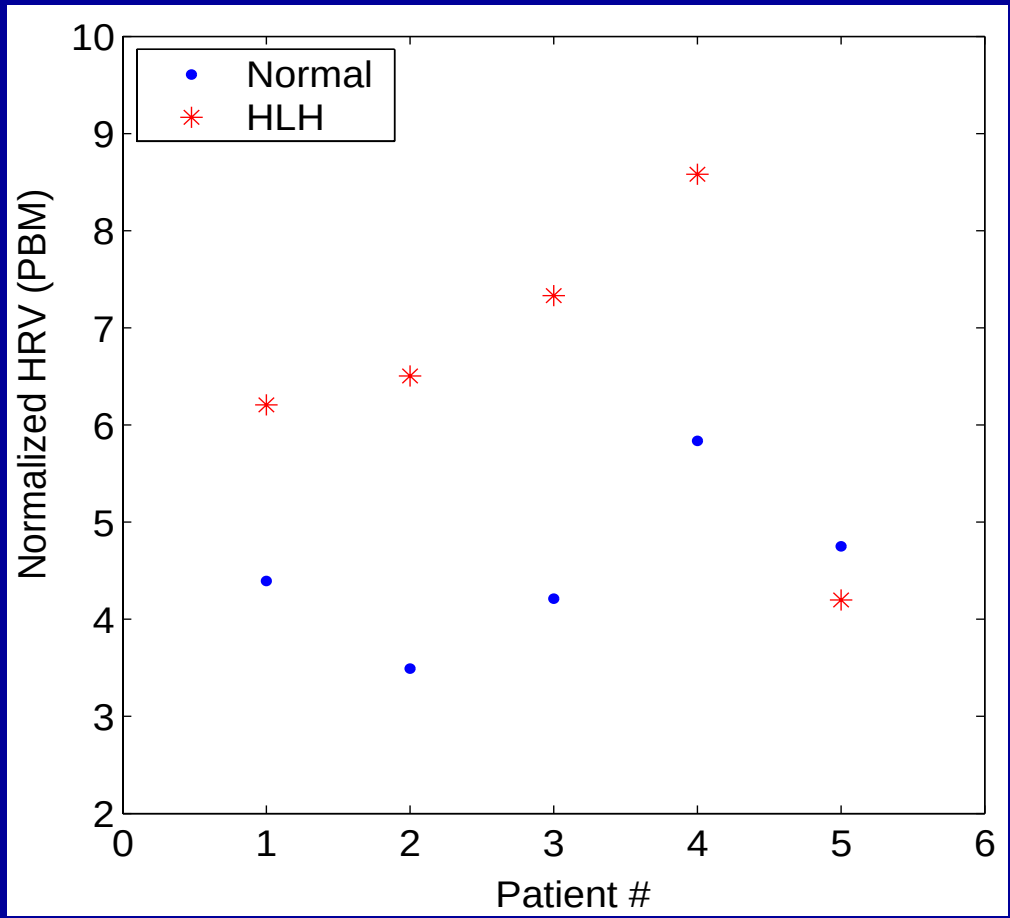


HRV for Monitoring Congenital Heart Defects

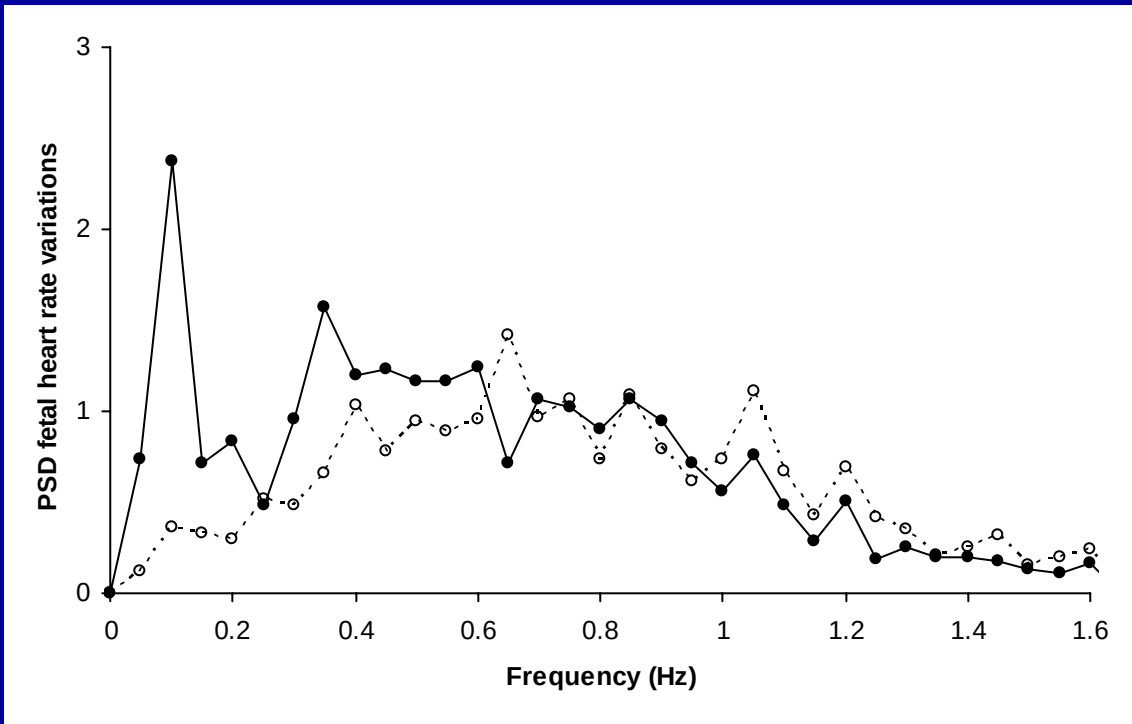


- Hypoplastic Left Heart syndrome: Left ventricle is under-developed, narrow aorta
- Extra work for right ventricle, and flow behavior is significantly affected
- We expect higher HRV than normal in this case

Application of HRV Measure to HLH

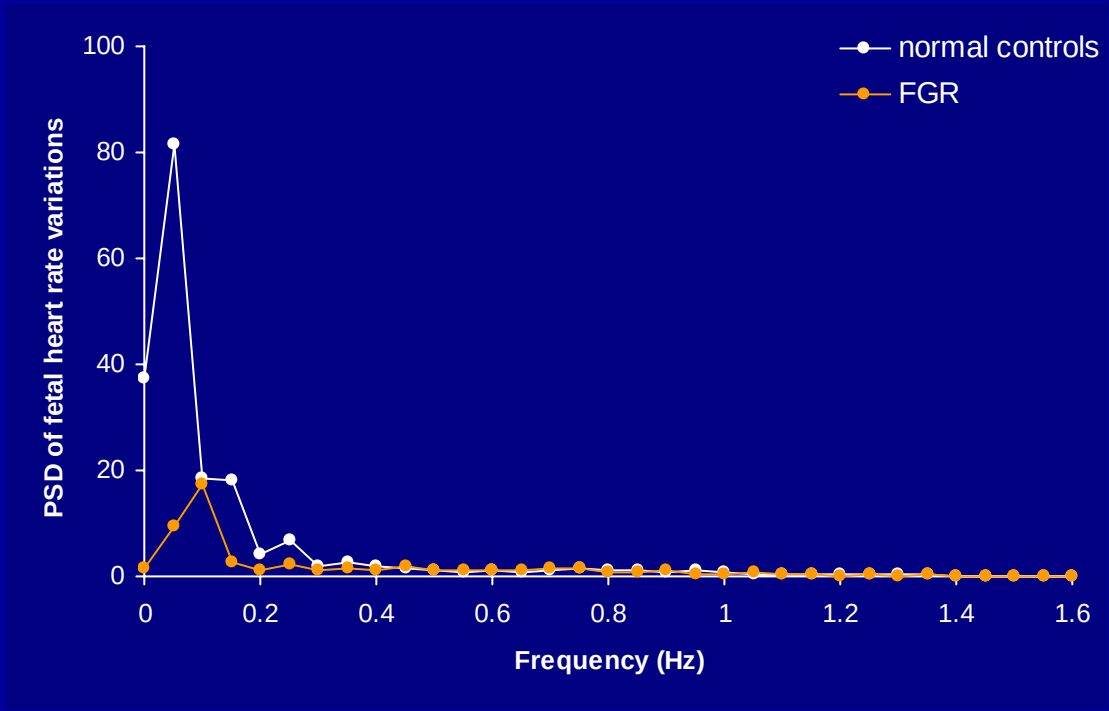


Power spectrum of heart rate variations



- Solid line: 15-20 weeks, Dashed line: 10-14 weeks
- Higher low frequency content in older fetuses

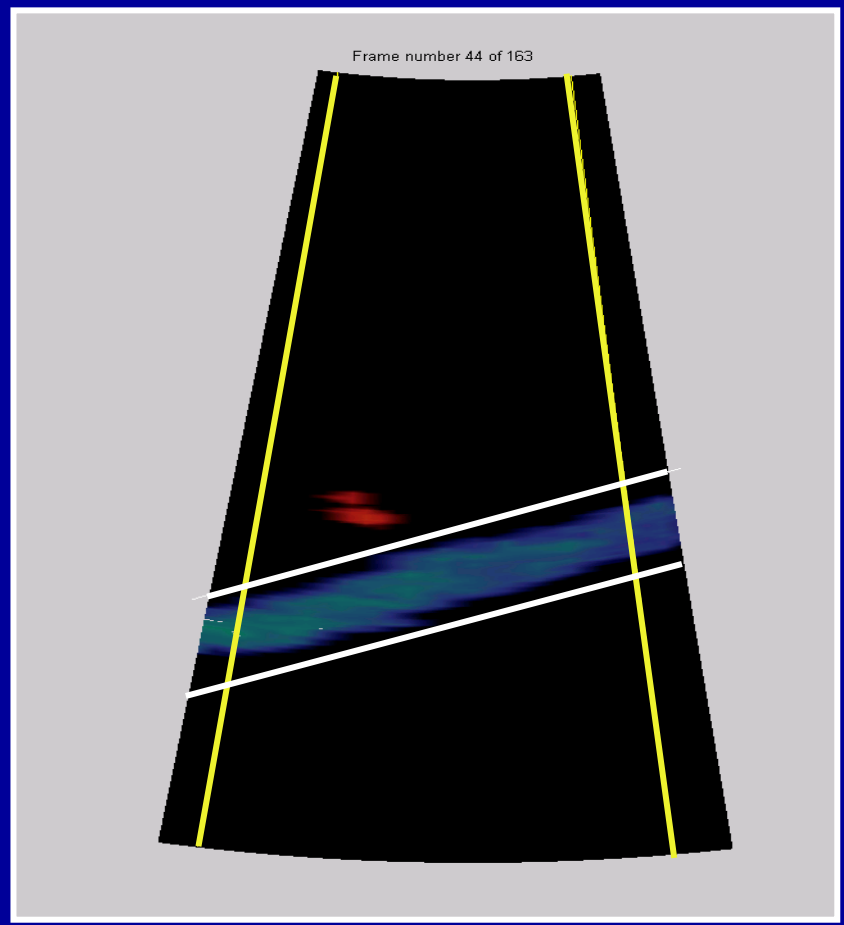
Power Spectrum of Heart Rate Variations Associated With Fetal Growth Restrictions



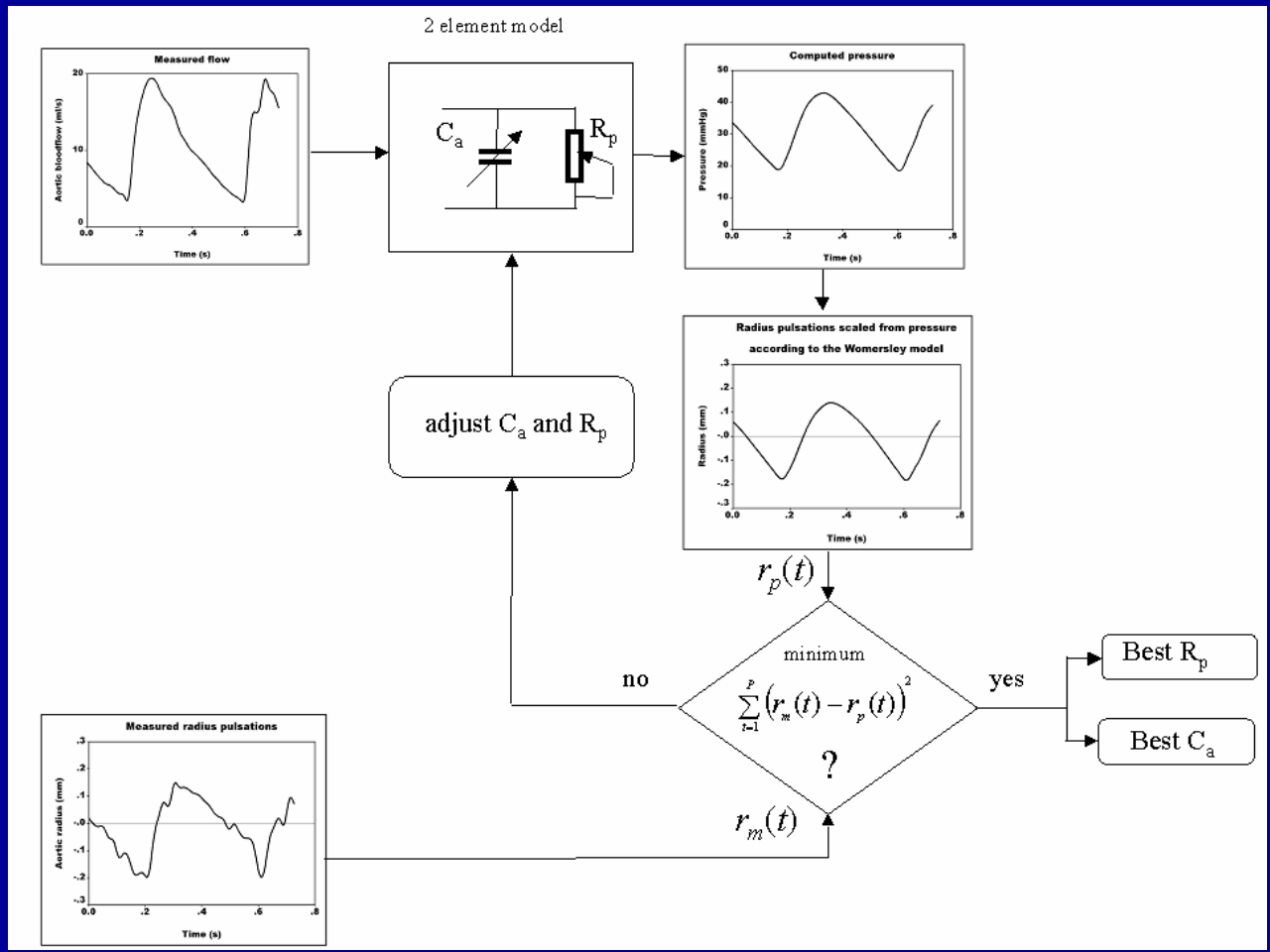
Estimation of Fetal Circulation Parameters From Color Doppler Data

Basics of Estimation from Color Doppler Measurements

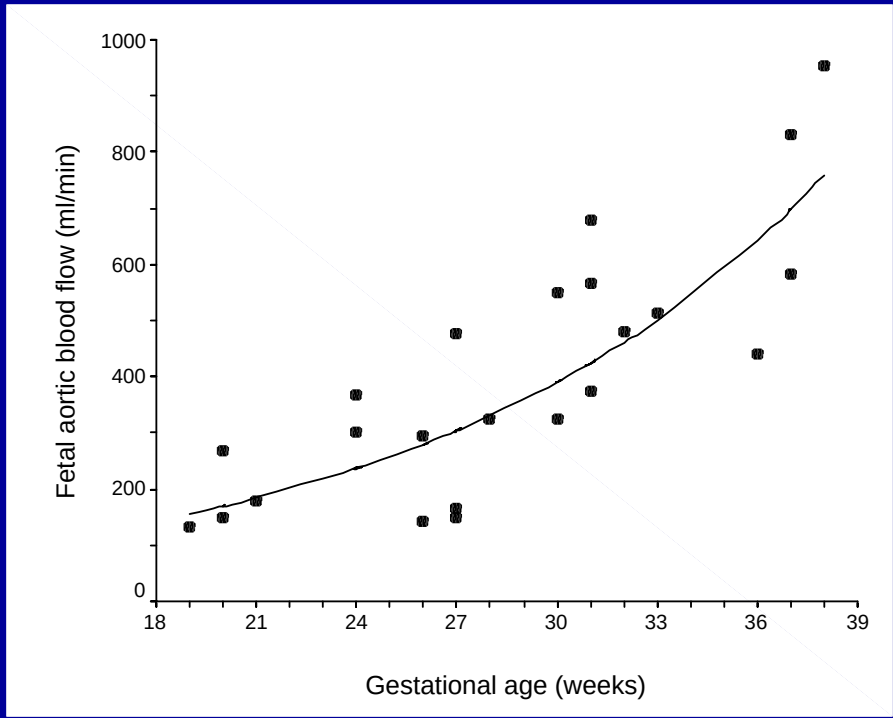
- Color Doppler with broadband beam forming and high frame rate provides good temporal and axial resolution
- Relatively easy to estimate and track wall boundaries over time
- Given the blood flow velocity information and the measured characteristics of the fetal blood vessel, we can estimate pressure, shear stress, flow volume, etc from color Doppler data



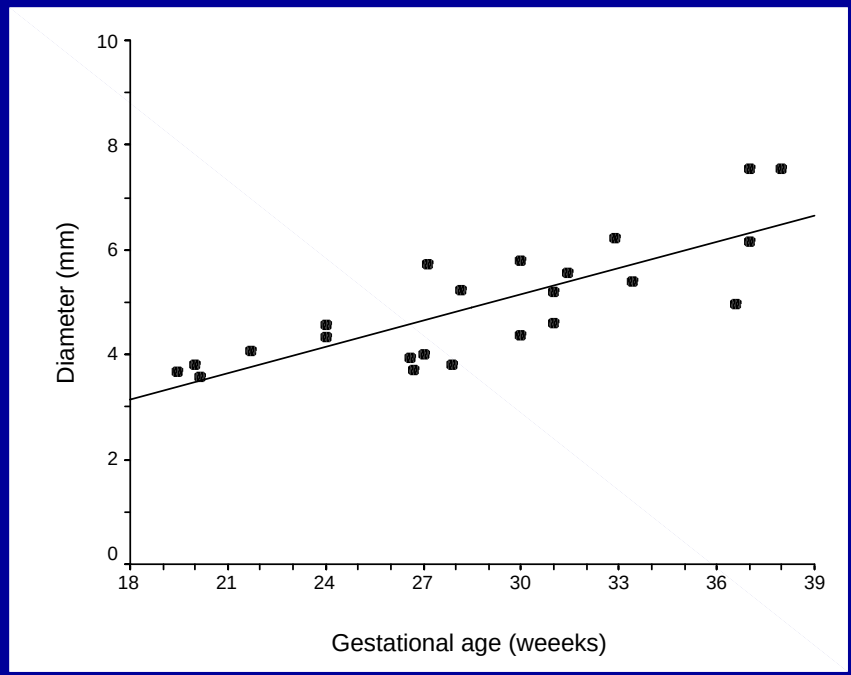
Measurement of Fetal Blood Pressure



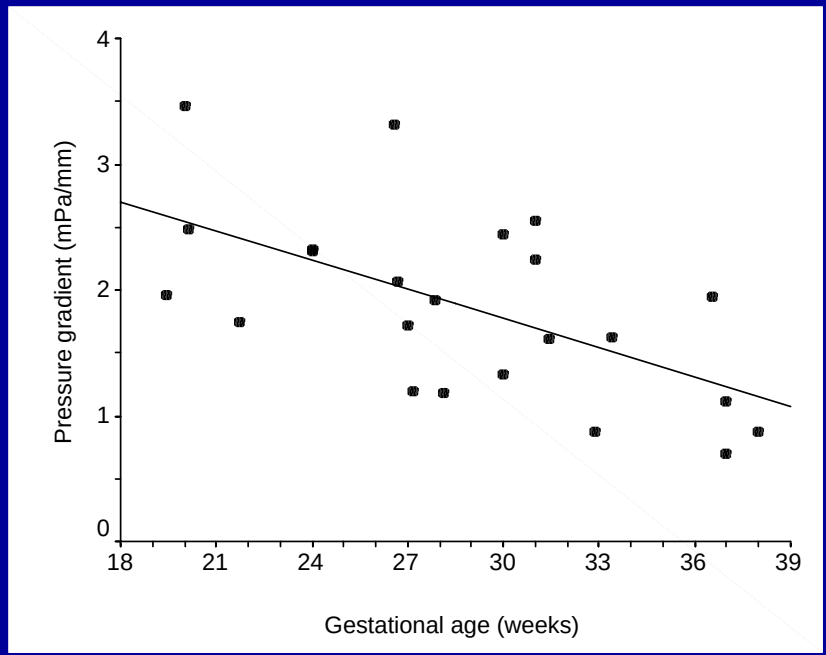
Log-linear Relationship Between Gestational Age and fetal Aortic Blood Flow



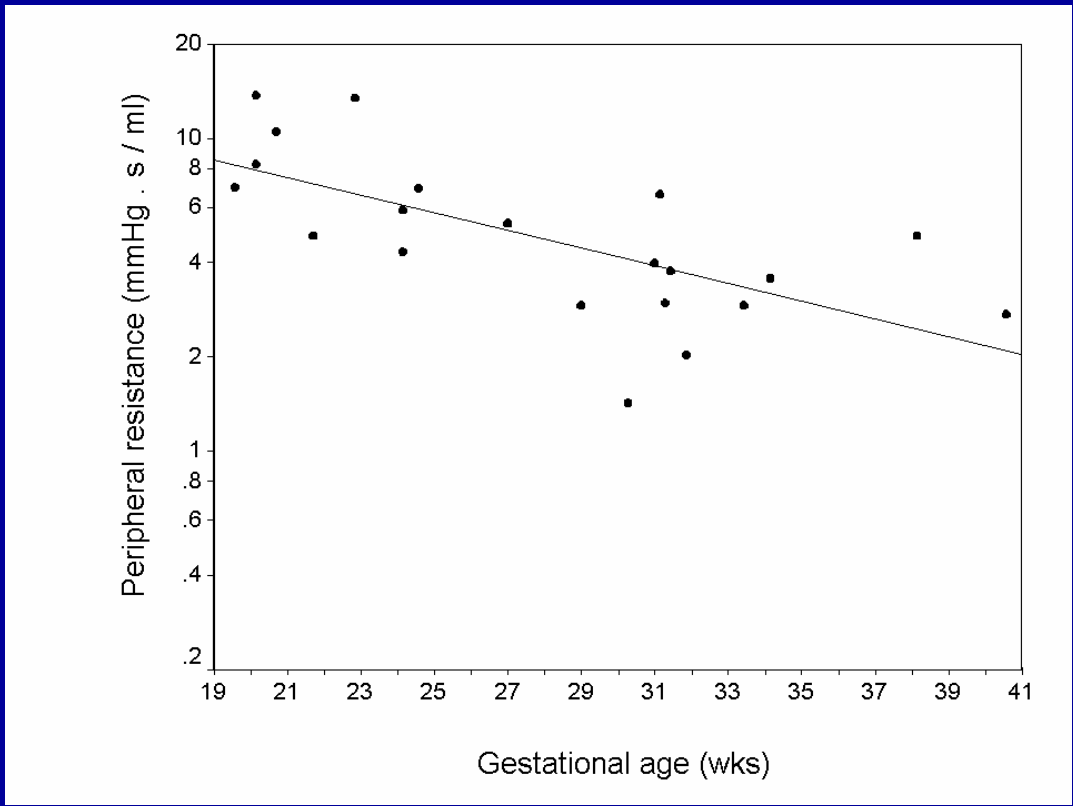
Fetal Aortic Diameter is Linearly Related to Gestational age



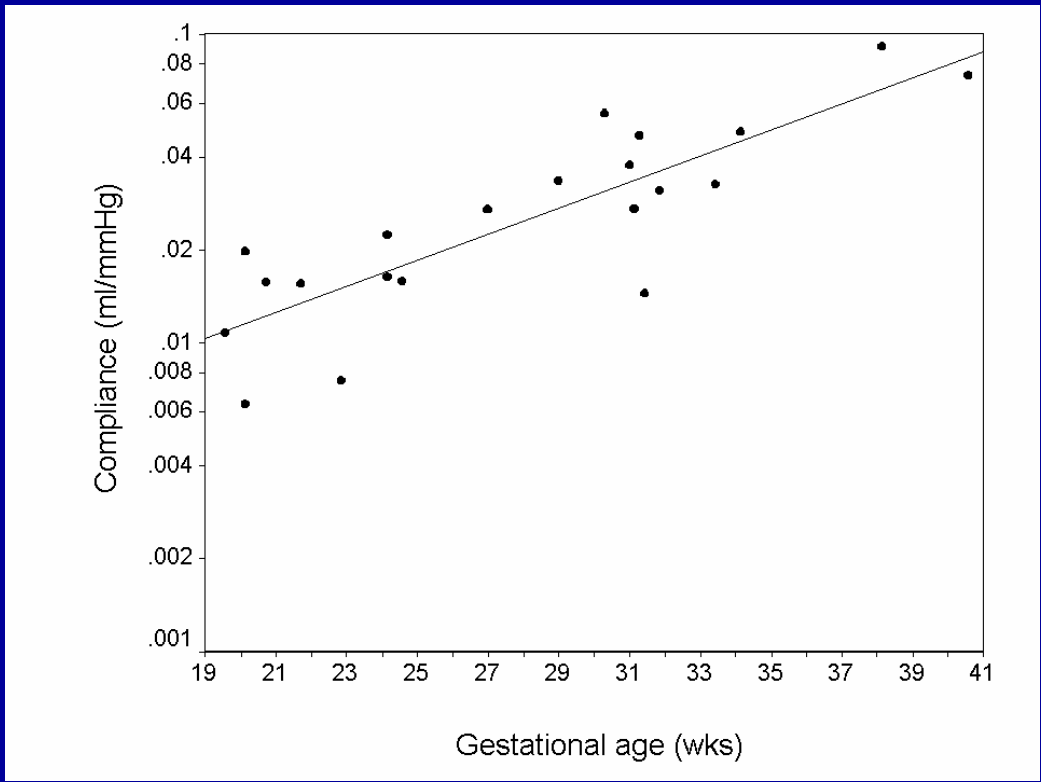
Pressure Gradient Decreases Linearly With Gestational Age



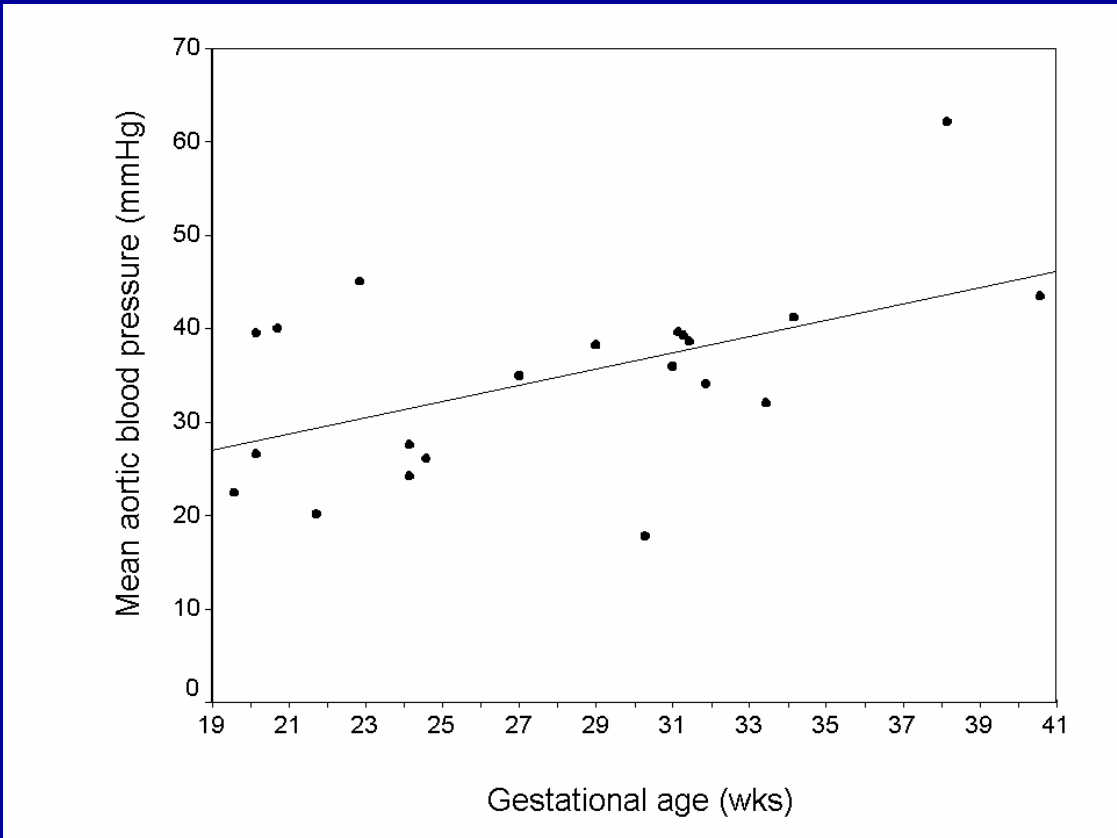
Gestational Age Vs Downstream Peripheral Resistance



Gestational Age Vs Fetal Arterial Compliance



Gestational Age Vs Mean Aortic Blood Pressure



Predicting Preeclampsia

Preeclampsia

- Preeclampsia is a disease that occurs only during pregnancy
- Affects both the mother and the baby. (Affects 5-8% of all pregnancies.)
- Characterized by high blood pressure and protein in the urine.
- Symptoms typically occur only in the late second or third trimester of pregnancy.
- Other possible symptoms: swelling, sudden weight gain, headaches and changes in vision
- Causes 50000-76000 deaths worldwide each year.
- The only known cure for preeclampsia is delivery of the placenta.

Preeclampsia in the USA

- Maternal illness
  - Hypertensive disorders complicate ~10% of all pregnancies. Approximate cost $3 billion
  - Maternal death: 18% of maternal death
- Infant illness
  - 15% of premature deliveries are caused by preeclampsia. Approximate cost $4 billion
  - Infant deaths: ~1200

Source: Preeclampsia Foundation

Status of Diagnostic Capabilities for Preeclampsia

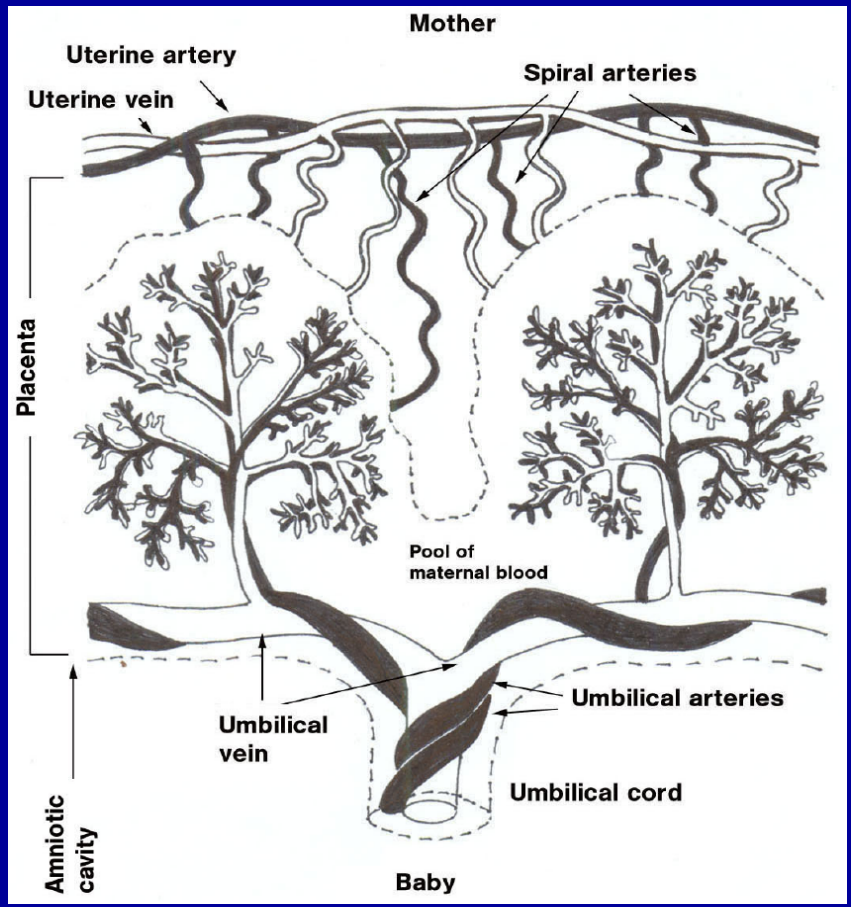
- Two thousand years after eclampsia was described, preeclampsia and eclampsia still complicate 10% of pregnancies yet their cause remains unknown. They are among the major contributors to maternal and perinatal morbidity and mortality worldwide. Preeclampsia/eclampsia is also associated with substantial health problems later in life in both women and their children. While the global financial burden is difficult to calculate, the immediate and long-term annual costs can be estimated as billions of dollars
  - Global Program to Conquer Preeclampsia/Eclampsia World Health Organization, 2002

Status of Diagnostic Capabilities for Preeclampsia (Cont.)

- "Ideally, the clinical diagnosis of preeclampsia would be based on sensitive and specific diagnostic tests derived directly from the causative mechanism of the disease. No such tests exist"

  -- Report of the Working Group on High Blood Pressure in Pregnancy, July 2000

A Possible Cause of Preeclampsia – Inadequate/Incomplete Trophoblast Invasion

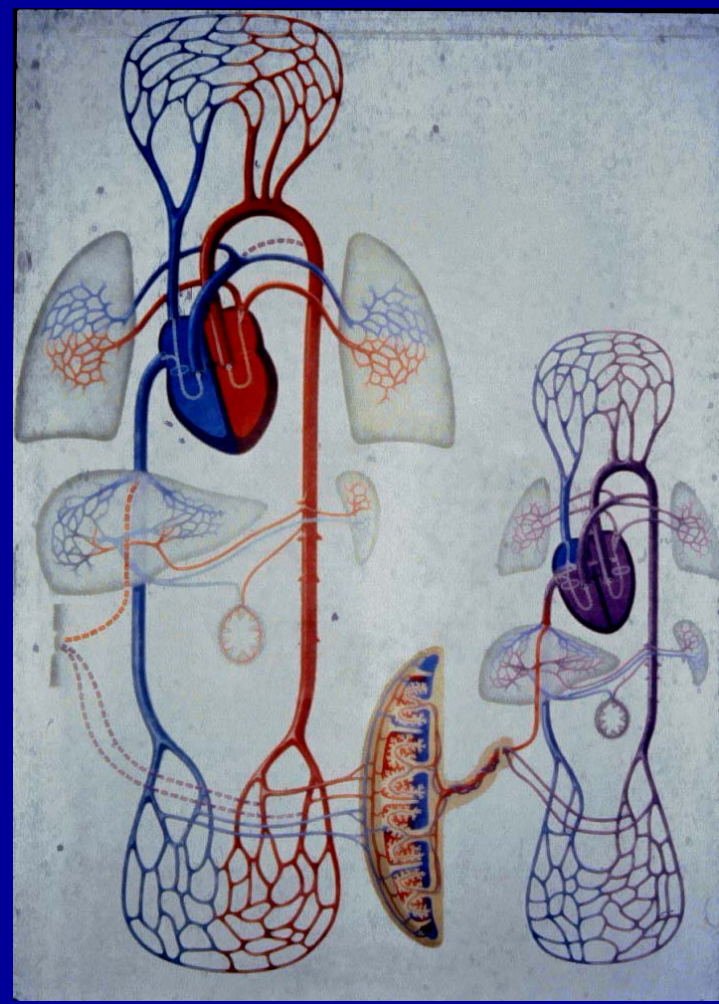


Endothelial Dysfunction Caused by Placental Insufficiency

- Endothelial cells line the inside of the blood vessels
- Increased endothelial cell size and apoptosis (programmed cell death)
- Oxidative stress (Presence of free radicals in excess of the capacity of the anti-oxidant defensive mechanisms)
- The increased size of the endothelial cells may be caused by the reduced shear stress caused by the blood flow at the vessel boundaries

Relationship Between Maternal and Fetal Circulations

- Because the maternal and fetal circulation systems are at least loosely connected through the placenta, we expect to see some correlation between the flow waveforms at the maternal and fetal heart rates.
- In preeclamptic pregnancies, the high resistance pathway created by insufficient trophoblast invasion might reduce this correlation.



Measuring Maternal Fetal Coupling Through Coherence Function

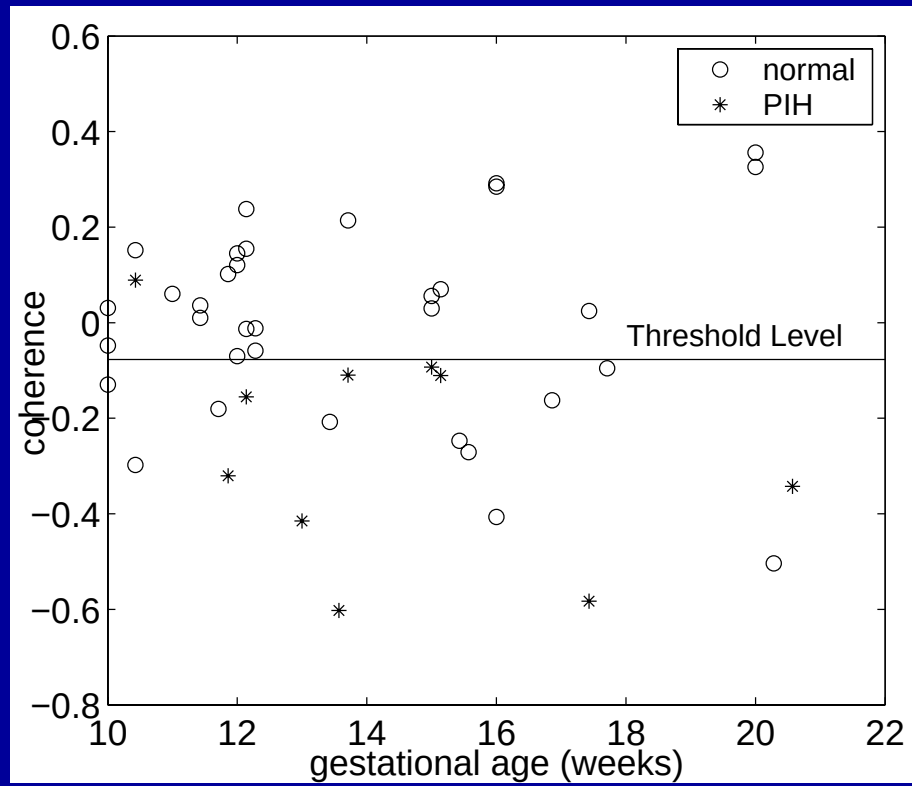
- Magnitude Squared Coherence Function

$$\gamma_{xy}(f) = \frac{\left|S_{xy}(f)\right|^2}{S_{xx}(f)S_{yy}(f)}$$

- Properties of MSC function
  - Values between 0 and 1
  - Time delay between the signals do not change the MSC function

Preliminary Results

- Analysis of sequentially acquired data
- Magnitude coherence values computed at maternal heart rate
- Gestational age dependent mean values have been removed from the MSC function prior to plotting
- Threshold level selected to maximize a weighted sum of sensitivity and specificity

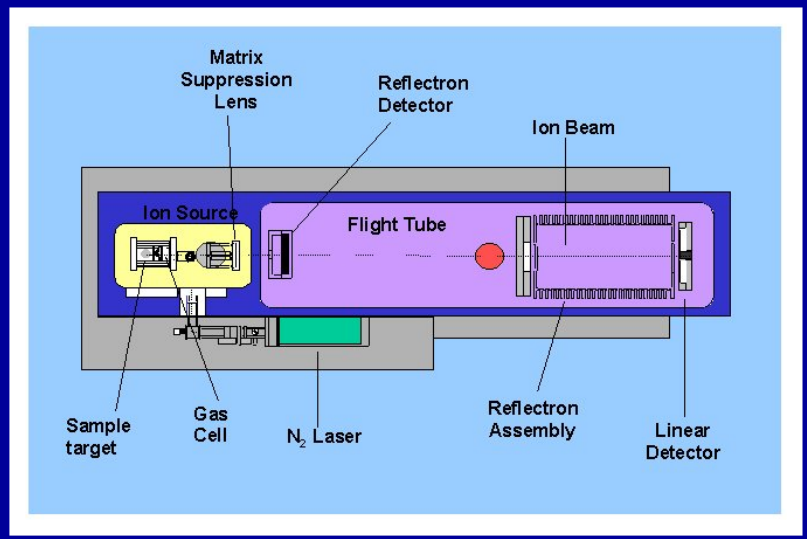


Multivariate Prediction of Diseases

Disease	Significant Variables	Sensitivity	Specificity
Preterm delivery (n=16)	Pulsatility index (Umbilical artery) Amniotic fluid index	69%	58%
Pregnancy-induced hypertension (n=9)	Pulsatility index (Umbilical artery) Amniotic fluid index Maternal heart rate	67%	87%
Preeclampsia (n=9)	Diastolic notch Coherence MHR Amniotic fluid index	78%	83%
Diabetis mellitus (n=7)	Coherence at MHR Maternal HR	71%	91%

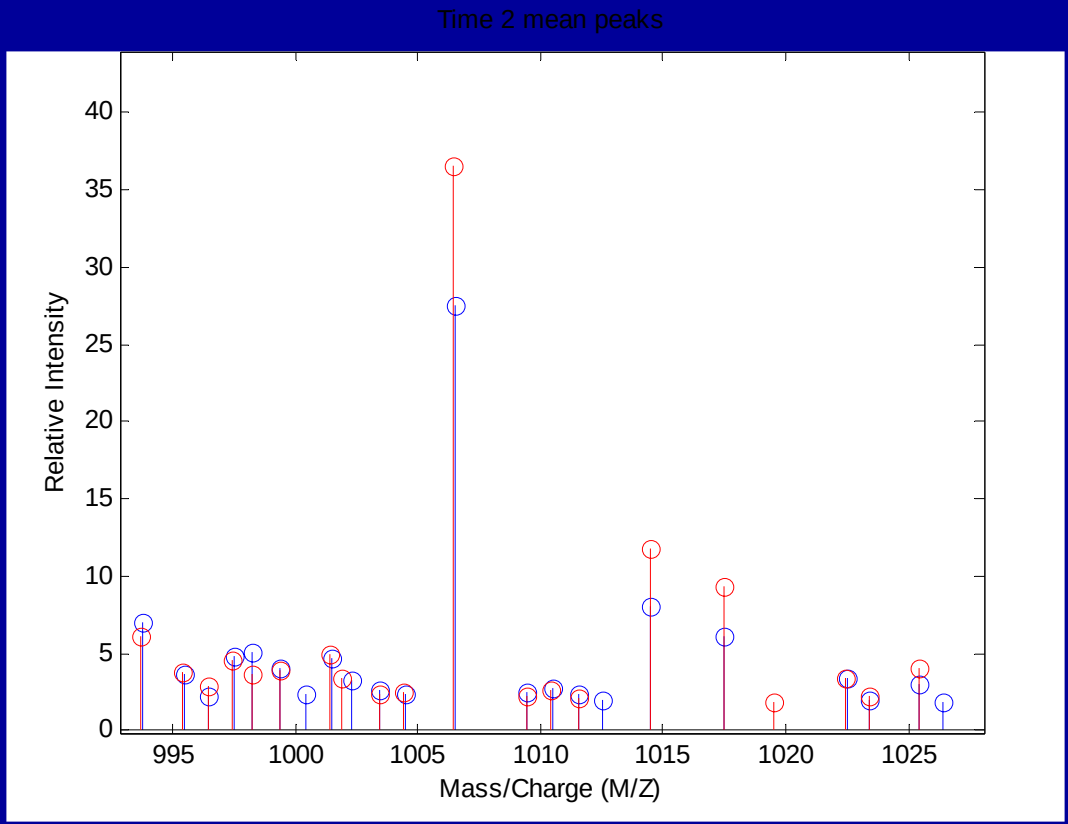
Proteomics for detecting maternal-fetal diseases

- Look for protein signatures that are only present in diseased states
- Detection of proteins using ion mobility spectrometry



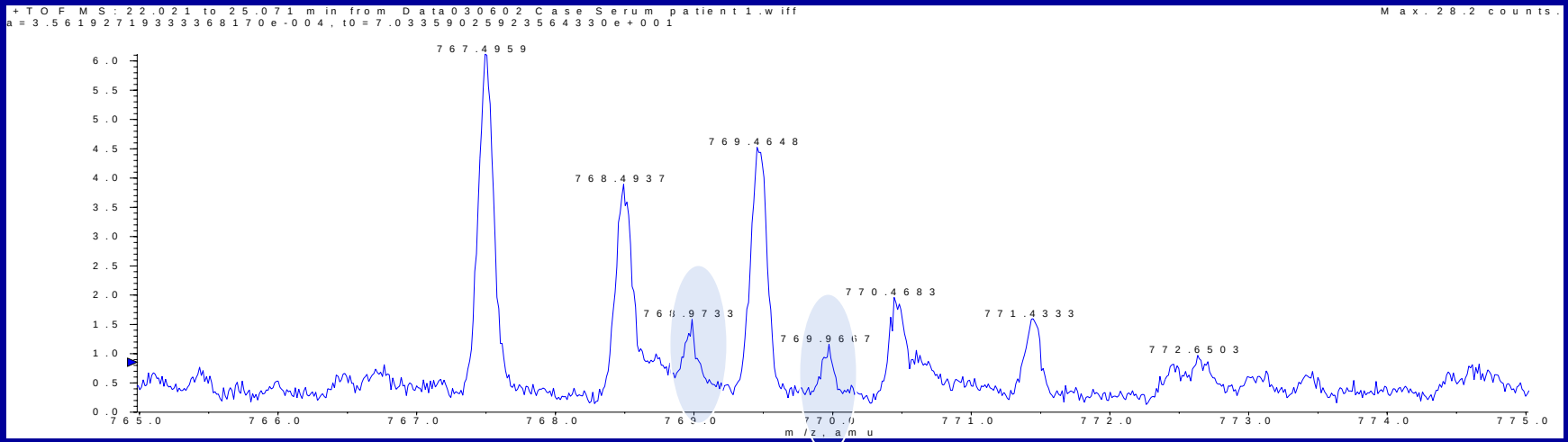
- Differentiates particles with different masses by their travel time in the tube.

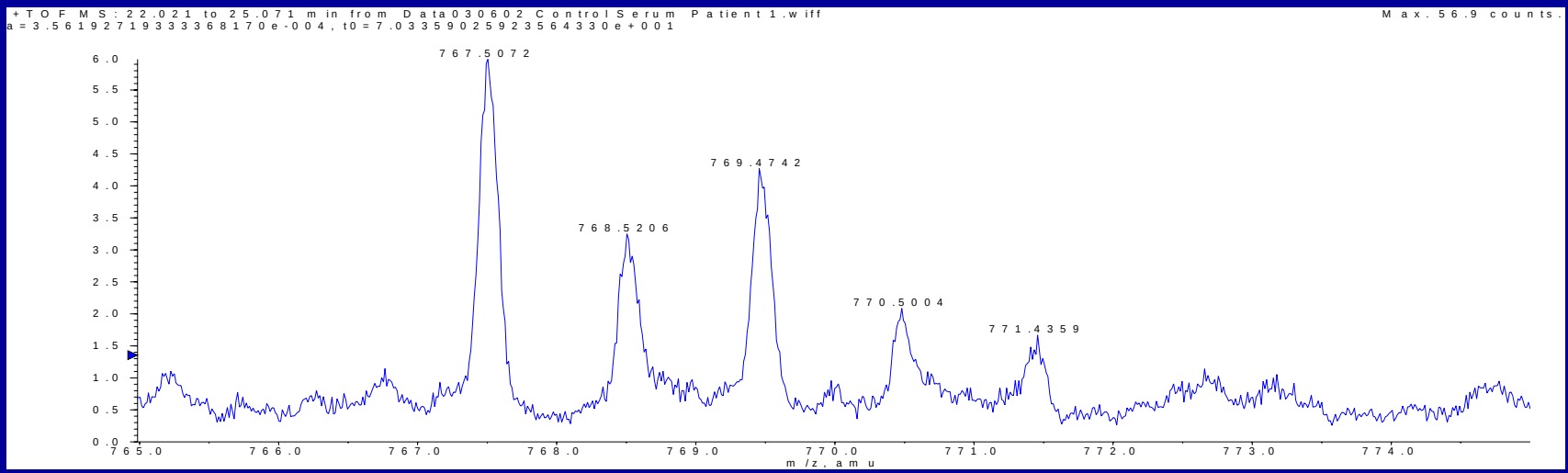
Protein Marker to Detect Preeclampsia?



- Sensitivity: 100% Specificity: 78%

Protein Marker to Identify Prematurity?





Concluding Remarks

- In spite of significant improvements in the care of the pregnant woman and her baby during the last century, there is much that still needs to be done.
- Characterizing the differences between waveforms acquired from women with normal pregnancies and from those suffering from fetal and/or maternal abnormalities will allow doctors to practice (engineering?) model based diagnosis and treatment.
- Signal processors can play a vital role in facilitating this.