Computational Medicine:

Oberon-based Simulation, Control, and Signal processing

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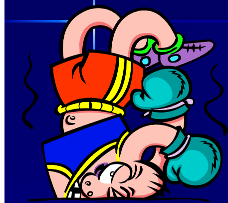
University Hospital Basel, Switzerland

Computers in Medicine



Disease understanding
Genomics/Proteomics
Disease simulation
Physiology simulation/modeling

Therapy
Drug development in silico
Therapy simulation/modeling

Imaging
Image acquisition
Image data flow
Image analysis
Image retrieval

Telemedicine

ID, personal data

Lab Tests
- data flow
- storage/retrieval
- analysis/interpretation
- privacy
- Array diagnostics

vital signs monitoring

Biosignals
-Signal processing
-Signal analysis
-Biosignals for machine control

The feedback loop of medicine

The patient → Data acquisition → Data processing → Making a diagnosis / Understanding of health & disease / Data interpretation → Management decisions (diagnosis, therapy) → The patient

Role of Oberon ?

Where we apply Oberon

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ETH Oberon wearable

Automatic ventilator control
Oberon, MatrixOberon, ETH Oberon wearable

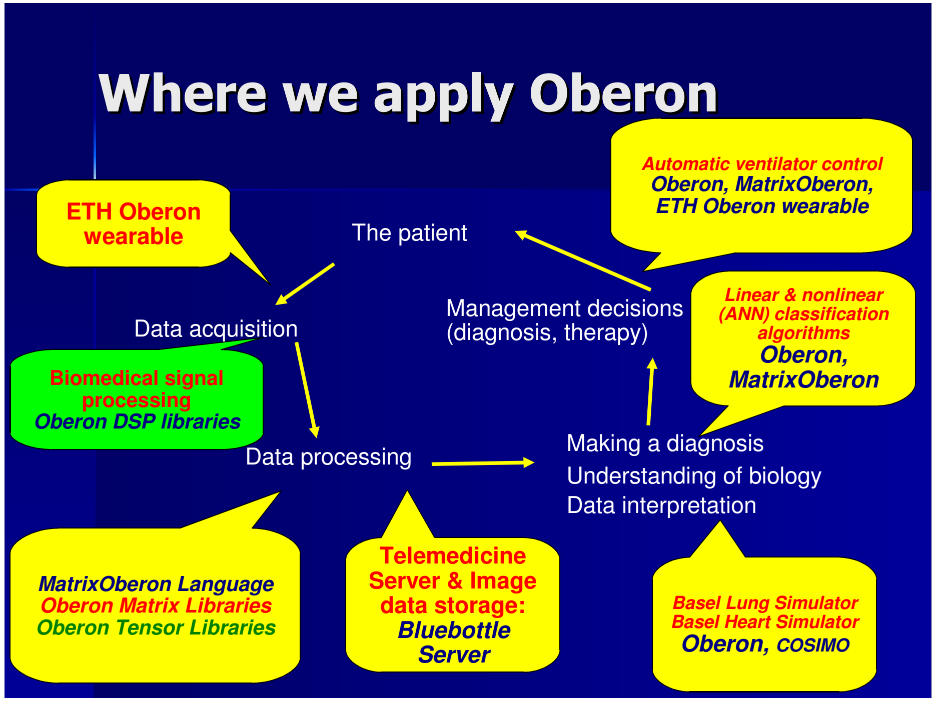
Biomedical signal processing
Oberon DSP libraries

Linear & nonlinear (ANN) classification algorithms
Oberon, MatrixOberon

MatrixOberon Language
Oberon Matrix Libraries
Oberon Tensor Libraries

Telemedicine Server & Image data storage:
Bluebottle Server

Basel Lung Simulator
Basel Heart Simulator
Oberon, COSIMO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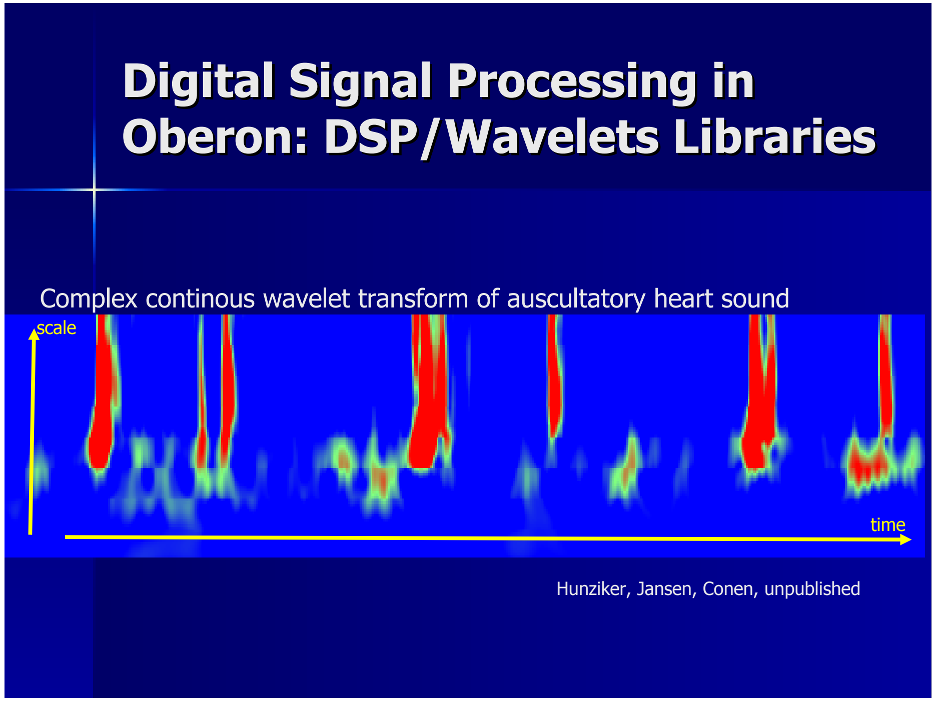
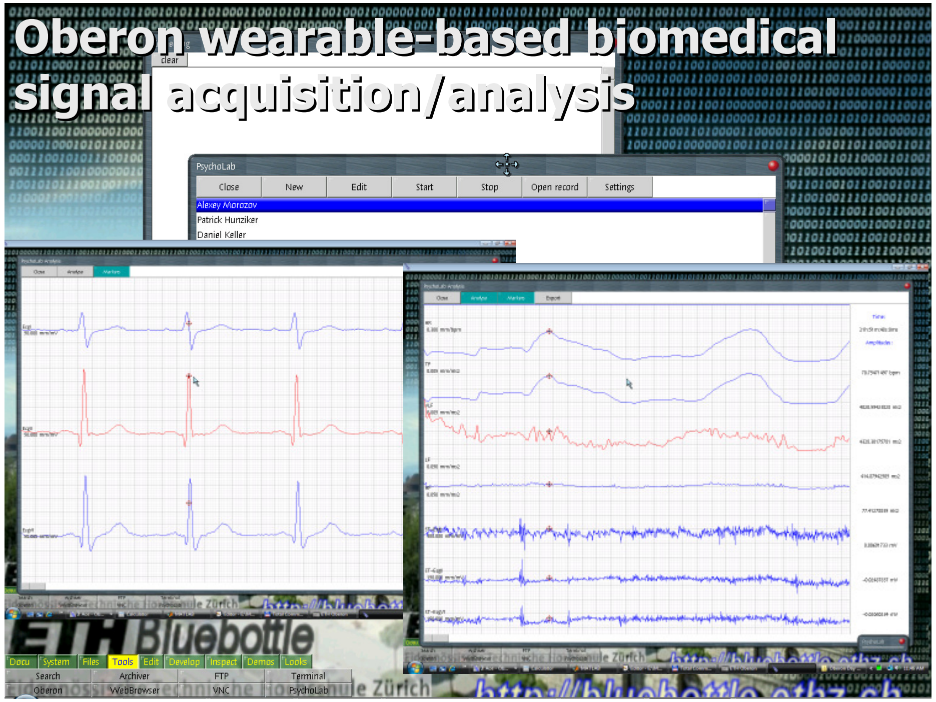
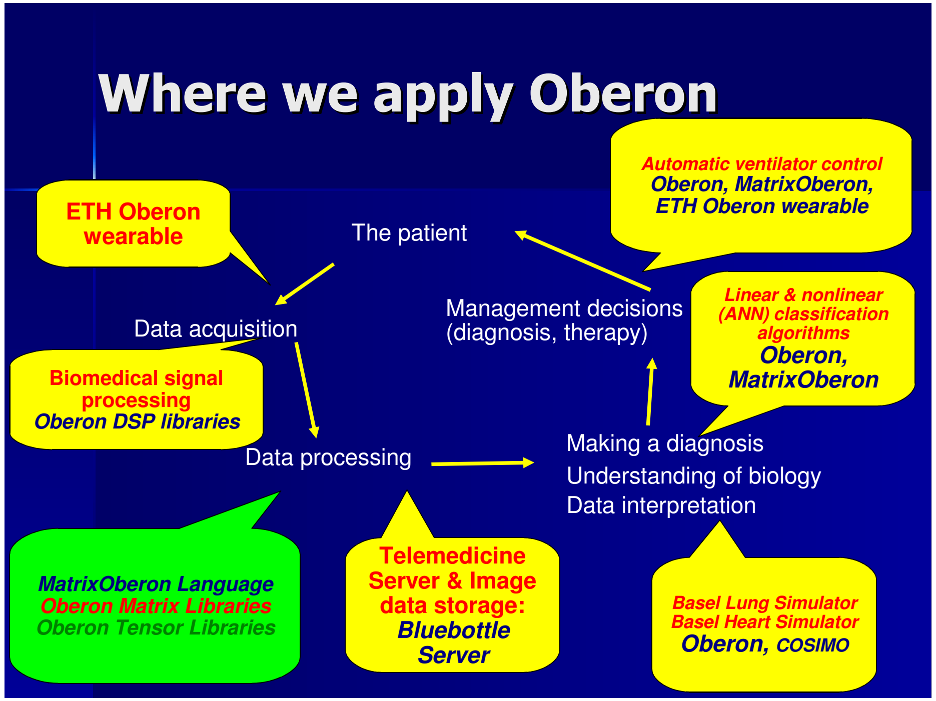

Digital Signal Processing in Oberon: DSP/Wavelets Libraries
Complex continous wavelet transform of auscultatory heart sound
scale
time
Hunziker, Jansen, Conen, unpublished


Oberon wearable-based biomedical signal acquisition/analysis
PsychoLab
Close
New
Edit
Start
Stop
Open record
Settings
Alexey Morozov
Patrick Hunziker
Daniel Keller
ETH Bluebottle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Matrix Libraries

- Based on MatrixOberon language (ETHZ)
  SIMD accelerated – multicore capable

- Linear Algebra Library (Uni Basel)
  MatrixBase
  MatrixTransforms *(Symmetric,Skew, Householder, ...)*
  MatrixStandardSolvers *(LU,Gauss-Jordan,QR,Cholesky)*
  MatrixIterativeSolvers *(Gauss-Seidel,Jacobi,SOR,CG)*
  MatrixMultigridSolvers *(AMG)*
  MatrixKrylovSolvers *(GMRES, GMRES(k), MINRES, ..)*
  MatrixPreconditioners *(SPAI)*
  MatrixOptim *(n-dim function minimization)*
  MatrixNeuralNetwork
  ...

Matrix Libraries - example

Pseudocode
(Wikipedia)

Choose an initial guess ϕ^0 to the solution
for k := 1 step 1 until convergence do
  for i := 1 step until n do
    $\sigma = 0$
    for j := 1 step until n do
      if j != i then
        $$\sigma = \sigma + a_{ij}\phi_j^{(k-1)}$$
      end if
    end (j-loop)
    $$\phi_i^{(k)} = \frac{(b_i - \sigma)}{a_{ii}}$$
  end (i-loop)
  check if convergence is reached
end (k-loop)

Implementation (incl SIMD)

```
MODULE MatrixDemoJacobi;

TYPE
  Matrix = ARRAY [ .. , .. ] OF LONGREAL;
  Vector = ARRAY [ .. ] OF LONGREAL;

  PROCEDURE Diag ( CONST A: Matrix): Vector;
  END Diag;

  PROCEDURE Inv ( CONST v: Vector): Vector;
  END Inv;

  (** Solve Ax=b  using Jacobi Algorithm.  *)
  PROCEDURE Jacobi*( CONST A: Matrix;  CONST b: Vector;  VAR x: Vector;  threshold: LONGREAL );
  VAR invd, d, r: Vector;
  BEGIN
    d := Diag( A );
    invd := Inv( d );
    LOOP
      r := A * x;  (* matrix-vector product. *)
      IF MathL.sqrt((r - b) +* (r - b)) < threshold THEN RETURN x END;  (* '+*' is inner product *)
      x := (b - r + d .* x) .* invd;  (* '.*' is elementwise product *)
    END;
  END Jacobi;

END MatrixDemoJacobi.
```

The need for Tensor(Multilinear) Tools

Nonregular sampled data:
an important problem in medical data analysis

- Patient monitoring:
  irregular measurement intervals

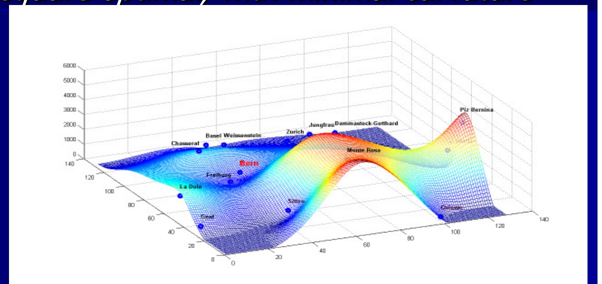
- Computer tomography:
  circular data acquisition, divergent X-ray beam

- 4D Ultrasound:
  "random" data from 3D space and time
  => resample to 3D moving dataset in regular grid

Simple example:

- Reconstruct map of Switzerland from arbitrary samples
  efficiently, least square optimal, with minimal curvature

10 cities
7 mountains



Solution:

-Cubic B-splines:
smooth interpolants with shortest support (->speed) and minimal curvature

- *regularized* (tolerate missing data) *least square problem*

Real world example

- [3D+t] data acquisition from beating heart
  1 second =
  - 128*128*32*32 =10^7 Samples at arbitrary location
  - 128*128*32*32 =10^7 cartesian grid points

    => sparse linear system
      size 10^7*10^7
      10^7 unknowns
      complicated sparsity pattern
    A high performance computation problem !
  - Suited for Oberon ?

The solution: multilinear (tensor) algebra in 'high performance Oberon'

- Analysis of the problem:
  - Original data share spatial connectivity which is +/- lost in matrix representation (sparsity)
  - This least squares problem $S^TSx=S^Tb$ is actually a tensor problem with

$$SU_{i,...} = \{g_{N-1}\}\otimes\{g_{N-2}\}\otimes\cdots\otimes\{g_0\}$$

"Standard linear algebra" *"Multilinear algebra"*

Ax = b

Matrix
Vector
Vector

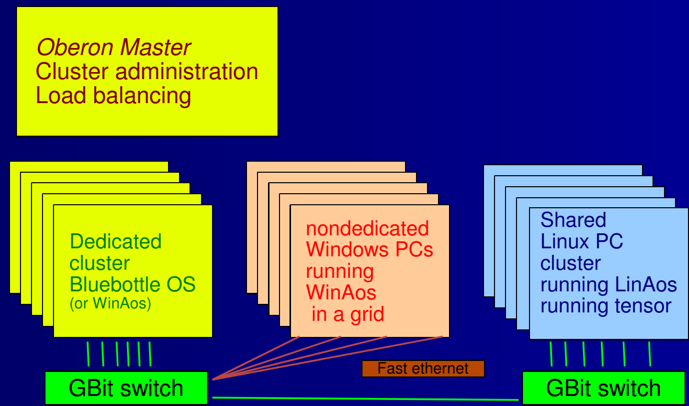
4D Structure
4D Structure
Multidimensional Structure

Tensor Oberon

- The language extension (ETHZ)

- The tensor algebra library
  - Data structures
  - Multilinear signal processing
  - Multilinear solvers

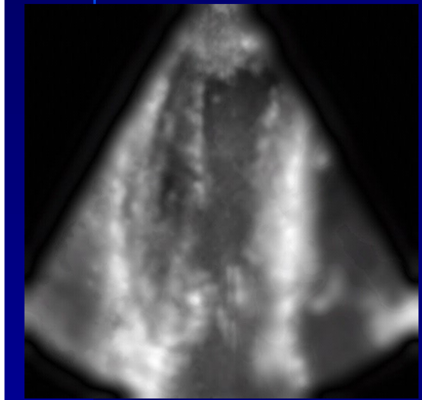
Grid/Cluster computation with Tensor Oberon



Tensor Oberon Results

- **4-Reconstruction of nonuniformly sampled data**

"Dynamic computed 4D Echo Tomography "

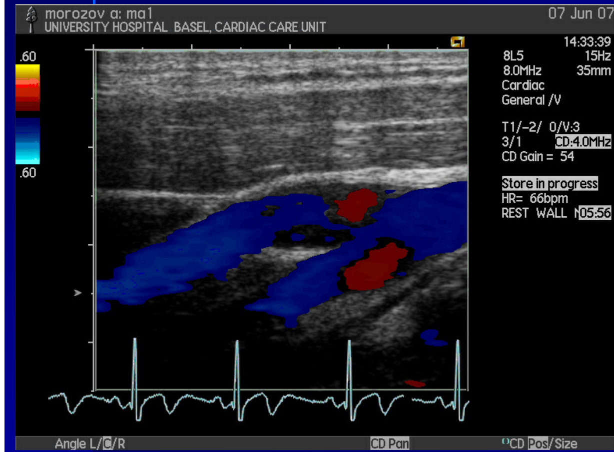


Data from new experimental transducer

- Flow field reconstruction from partial image information

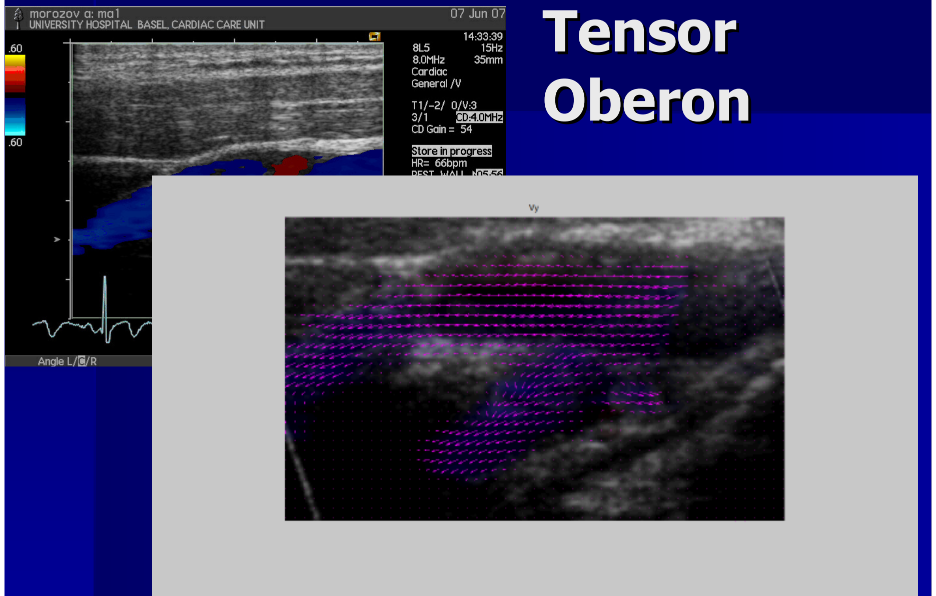
Results Tensor Oberon

Doppler flow information:
only velocity projection along ultrasound beam available



- Flow field reconstruction from partial image information

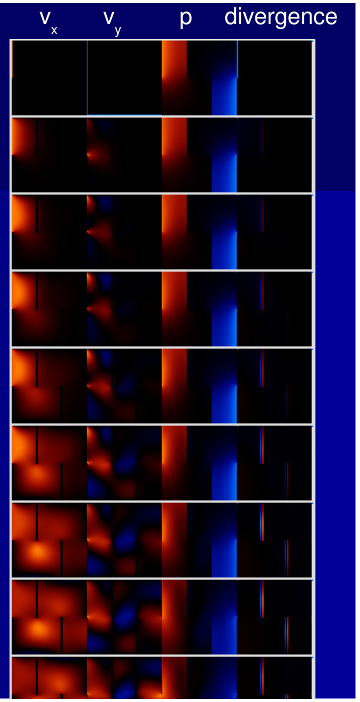
Results Tensor Oberon



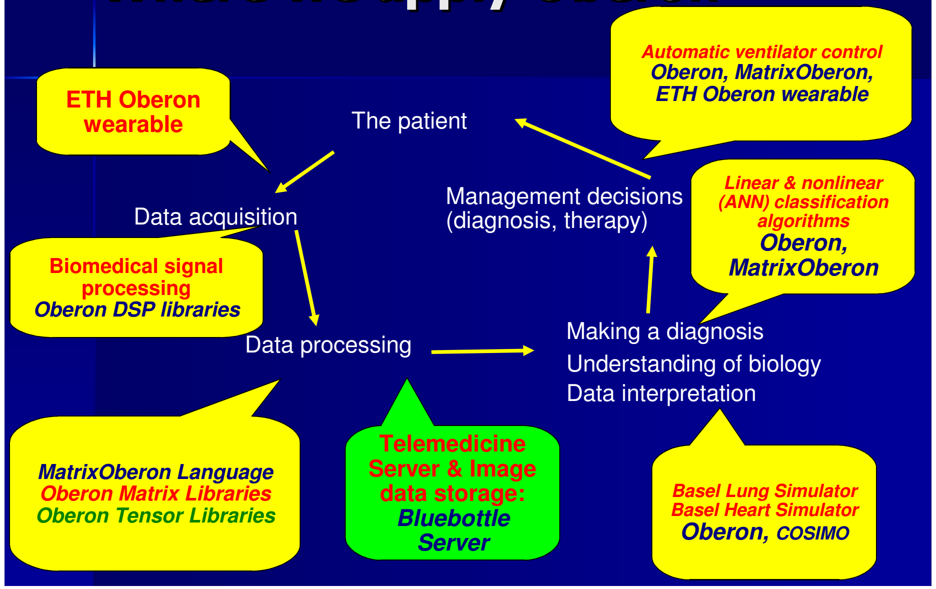
Results

- Implementation of
  Navier Stokes Equations
  for computational fluid dynamics
  of circulation

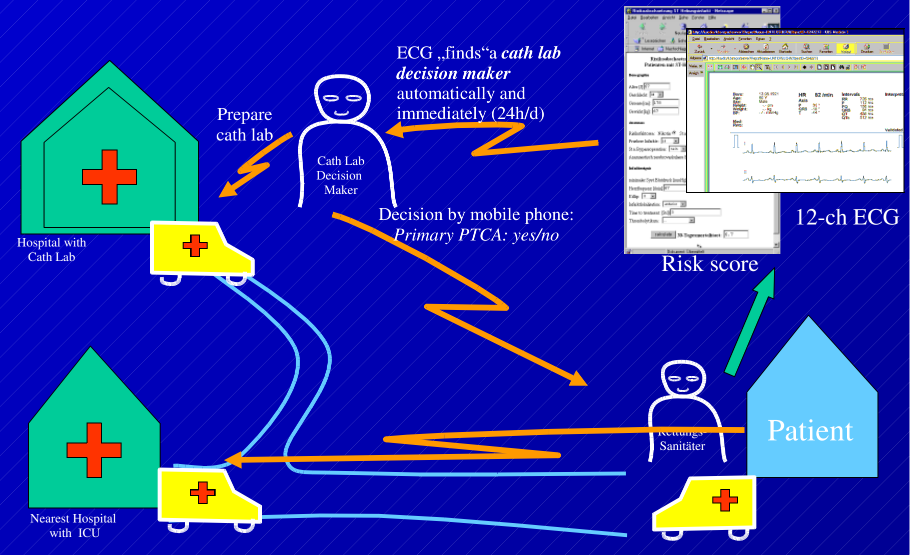
  MatrixOberon language extension
  Oberon Matrix Libraries
  Oberon DSP Libraries



Where we apply Oberon



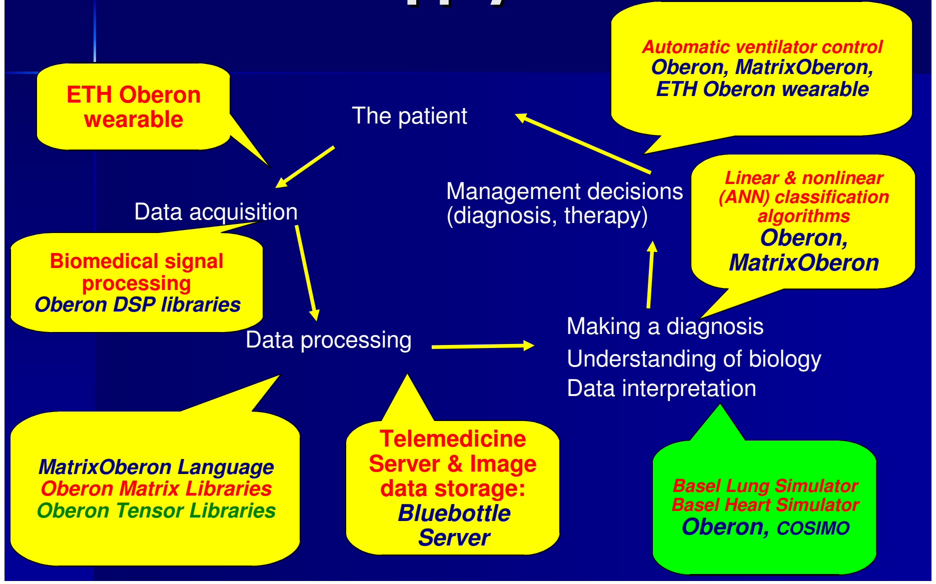
The Basel Telemedicine Concept:



Patient A.B. Prähospital EKG

Zeit: 3 min

Where we apply Oberon



Background of lung simulation

Clinical studies with new strategies to treat patients with lung disease, but we realized that it is difficult to understand what is going on in the patient

Simple mechanical lung models. *disappointing* yielding very different results from what is observed in patients.

Clinical studies : *conflicting results:*
- improvement in volumes, pressures
- few effects on blood gases

Structure of the bronchial tree in man

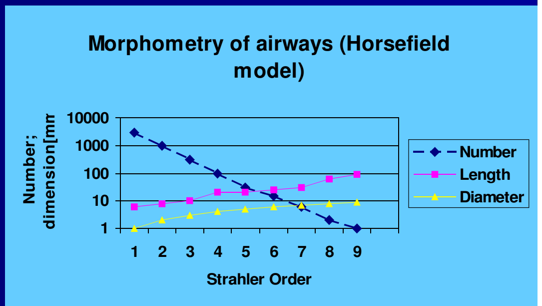
Several morphometric models:
Symmetric <-> asymmetric <-> monopodial
Connected <-> not connected

Model of Weibel, 1963
Symmetric, connected
most widely used

Model of Horsefield, 1971:
Asymmetric, connected

Model of Yeh, 1979:
Symmetric, not connected

Model of Ross 1957:
asymmetric, not connected



Key pathophysiological characteristics of airway disease:

- **narrowing of airways,**
  - **predominantly distal (COPD)**
  - **or proximal (larynx edema, obstruction; Asthma)**
- **Inhomogenous pathology in different parts of lung**
- **Laminar versus turbulent flow conditions**
- **Air trapping (dynamic over-inflation)**
- **Dynamic airway collapse**
- **Secretions**

complex physics ! Is simulation feasible ?

Fluid dynamics of air flow

Laminar flow conditions: *Hagen-Poiseuille Equation*

pressure loss depends on airway radius, length, gas viscosity;
minor influence of surface roughness

$$dP = \frac{V 8 \eta \ell}{\pi r^4}$$

Turbulent flow conditions:

pressure loss depends on airway radius, length, gas density
strong dependence of surface roughness

$$dP \approx V^2 \rho$$

Probability of laminar versus turbulent flow:

Depends on Re (Reynold's number), which is made up of
Gas Velocity, Gas Density, Diameter, XX

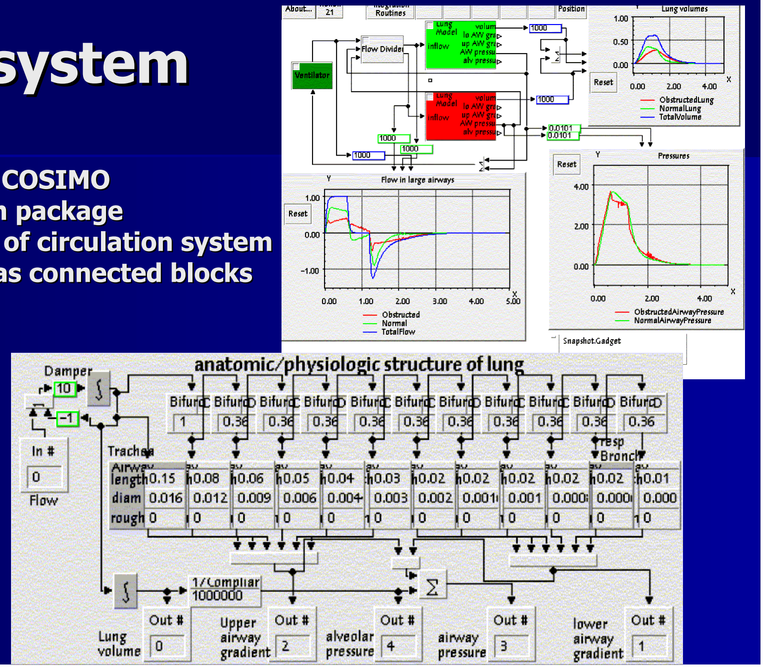
$$Re = \frac{2 r \rho v}{\eta}$$

Pressure loss at bifurcations

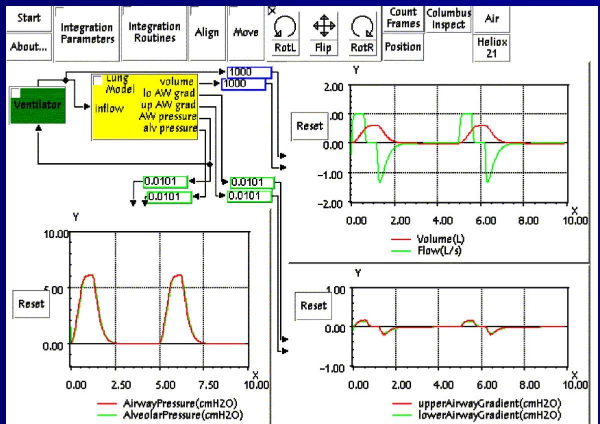
Depends on bifurcation shape, angle, XX

The system

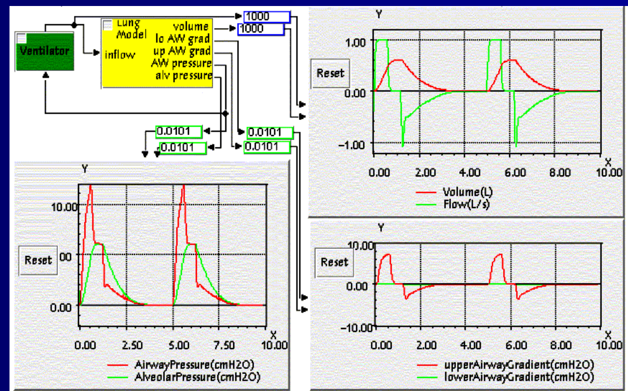
-based on COSIMO Oberon package
-elements of circulation system modelled as connected blocks



The normal lung

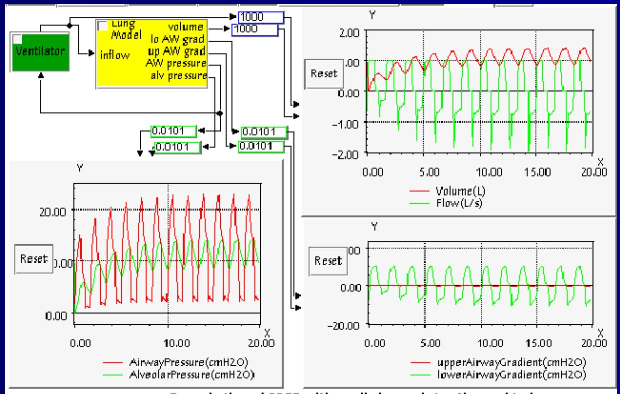


The small endotracheal tube/ tracheal obstruction



normal lung with 6mm orotracheal tube leading to inspiratory and expiratory upper airway gradient and prolonged expirium

The combination of lung disease (COPD) and fear (rapid breathing) leads to dangerous dynamic hyper-inflation of the lung



Exacerbation of COPD with small airway obstruction and tachypnea leading to air trapping

Conclusions

- Real-time simulation of lung disease based on computational fluid dynamics is feasible
- yields ventilation patterns that correspond to those observed in real patients with well-defined airway disease
- allows quantitative assessment of new ventilation strategies
- resulted in new insights in effects of Helium ventilation in COPD patients
- will allow training in ventilation management of patients with airway disease on the ICU without danger for the patients

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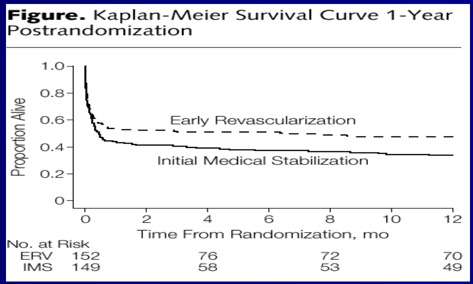
Catheter-based pumps in shock:

Prediction of efficacy by computational disease modeling and clinical observations

Cardiogenic Shock: a highly lethal syndrome

Mortality 50-70 %



SHOCK trial, Hochmann, JAMA 2001

Survivors of the acute phase of AMI with shock have a realistic chance for long-term survival

=> Do everything to give them this chance

Physiology of shock in AMI

Healthy myocardium: can be stimulated

Necrotic myocardium: no recovery. High wall stress stretches necrosis => early dilatation in AMI

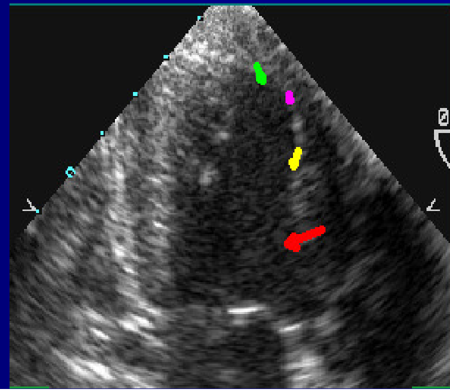
Stunned myocardium: able to recover, but late (hours to days)

Ischemic myocardium in border zone: able to improve or to worsen rapidly

Myocardium in remote territories with CAD: potential for ischemia

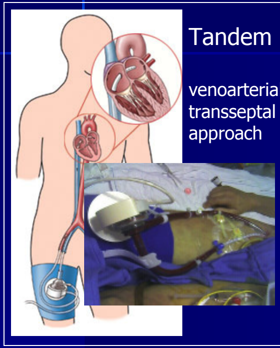
Suehling, Hunziker, Circulation 2005

Shock physiology in AMI is complex



Understanding is key to rational treatment.

percutaneous mechanical support



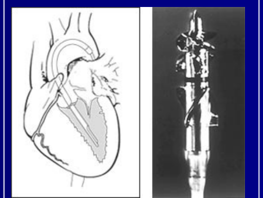
Tandem Heart

venoarterial transseptal approach

Lifebridge – inguinal, veno-art. access portable heart-lung support system

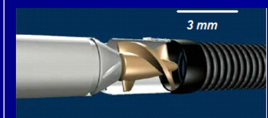
Catheter based axial pumps – transaortic approach

Nimbus Hemopump

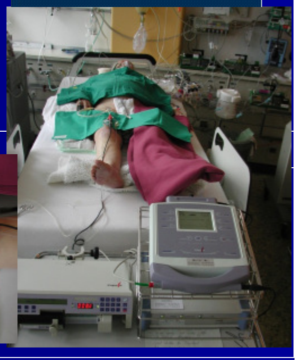


F14. Ext motor. up to 1.5-2L/min. Urban et al

Impella Recover

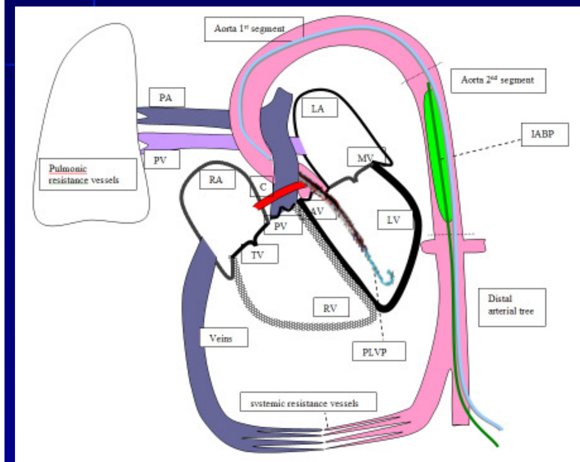


F12 (2.5L/'), F21 (5L/')



The Basel Heart Simulator

Computational fluid dynamics simulation of the cardiovascular system



A system of differential equations for mathematical modeling of multiple segments of the circulation based on in vivo- data.

Full biomechanical modelling:
heart, arteries, peripheral circulation & venous system

- Impact of
- systolic & diastolic abnormalities,
- ischemia,
- drug effects &
- assist devices

can be studied.

Hunziker & al, 2006

Modeling: Numerical Integration

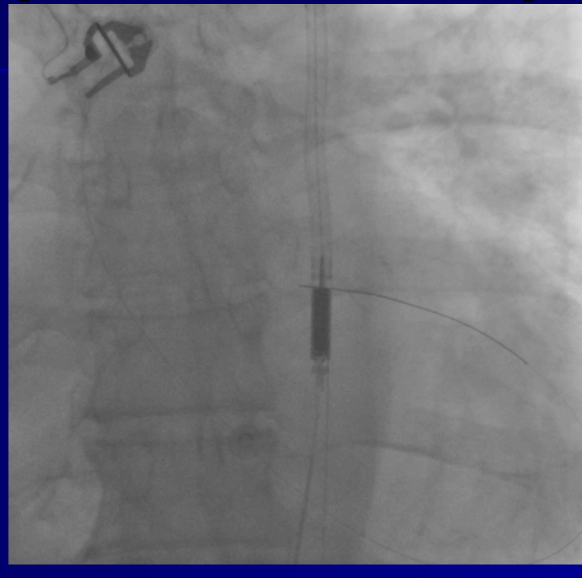
```
PROCEDURE Init;
BEGIN
  Integrator.Dynamic := Dynamic;
  Integrator.Integ := IntegDP54.DormandPrince54;
  horizon:=0.3;

  Integrator.InitLists;
  V10:=LVVd; V20:=AoV0/3; V30:=AoV0/3; \
  Signals.DeclStateSignal(V1, I1, V10, horiz
  Signals.DeclStateSignal(V2, I2, V20, horiz
  Signals.DeclStateSignal(V3, I3, V30, horiz
  Signals.DeclStateSignal(V4, I4, V40, horiz
  Signals.DeclStateSignal(V5, I5, V50, 0);
  Signals.DeclStateSignal(V6, I6, V60, 0);
  Signals.DeclStateSignal(V7, I7, V70, 0);
  Signals.DeclStateSignal(V8, I8, V80, 0);
  Signals.DeclStateSignal(V9, I9, V90, 0);
  Signals.DeclStateSignal(VA, I10, VA0, 0);
  Signals.DeclStateSignal(W1, w1, W10, 0)
  Signals.DeclStateSignal(W2, w2, W20, 0)
  Signals.DeclStateSignal(W3, w3, W30, 0)
  Signals.DeclStateSignal(W4, w4, W40, 0)
  Signals.DeclStateSignal(W5, w5, W50, 0)
  Signals.DeclStateSignal(CorP, corP, CorP(
  Signals.DeclStateSignal(Viabp, Iiabp, 0, 0
  Signals.DeclStateSignal(CO, co, 0, 0);
  Signals.DeclStateSignal(MAP, P2, 0, 0);
  Signals.DeclStateSignal(PAP, P8, 0, 0);
```

```
(*Resistances*)
R1 := AVstate(P1, P2, oldAorticValveState);
(*IF (oldAorticValveState=AVRo) & (R1=AVRc) THEN LVESV:=Signals.InterpolateSignal(sV1,Integrator.time-0.01);END; (*aortic valve has just closed*)*)
IF V1<LVESV THEN LVESV:=V1 END;
oldAorticValveState:=R1;   (*aortic valve resistance, a function of valve opening*)
R2 := AoR;   (*proximal->distal aortic resistance*)
R3 := AoR;   (*Arterio-preArteriolar Resistance*);
R4 := PeripheralResistance(Vasoconstriction/Vasodilators);   (*systemic vascular resistance, not including aorto-arterial segment*)
R5 :=  SvRaResistance; (*resistance between veins and RA*)
R6 := TVstate(P6, P7, oldTVState); oldTVState:=R6;   (*tricuspid valve*)
R7 := AVstate(P7, P8, oldPVState); oldPVState:=R7;   (*pulmonic valve*)
R8 := PVR /Vasodilators;
R9 := PvLaResistance;
R10 := MVstate(P10, P1, oldMVState);
IF (oldMVState=MVRo) & (R10=MVRc) THEN
  LVEDP:=Signals.InterpolateSignal(sP1,Integrator.time-0.01);
  LVEDV:=Signals.InterpolateSignal(sV1,Integrator.time-0.01);
END; (*MV has just closed*)
oldMVState:=R10;   (*mitral valve*);

i12 := (P1-P2 - di12dt*L12 )/R1; (*i12:=symmetricSigmoid(i12/i12Max)*i12Max;*) (*aortic valve flow*) (*Resistance - Inductance, serial; *) (*limit sho
i12B := (P1-P2 - di12dt*L12 )/R1; (*i12B:=symmetricSigmoid(i12B/i12Max)*i12Max;*)
i23 := ((P2-P3) (*- di23dt*L23*) )/R2;     (*flow from proximal aorta to distal aorta*)
i23B := ((p2-p3) (*- di23dt*L23*) )/R2;
i34 := ((P3-P4) (*- di34dt*L34*) )/R3;   (*flow from distal aorta to arteries*)
i34B := ((p3-p4) (*- di34dt*L34*) )/R3;
i45 := (P4-P5)/R4;   (*peripheral resistance*)   (*flow in organs*)
i56 := (P5-P6)/R5; (*inflow vein->right atrium*)
(*i61 := (P6-P1)/R6;*)   (*flow across tricuspid valve in case of univentricular circulation*)
i67 := (P6-P7)/R6;   (*flow tricuspid valve in case of biventricular circulation*)
i78 := (P7-P8)/R7;   (*flow across pulmonic valve*)
i89 := (P8-P9)/R8;   (*flow across pulmonary vascular bed*)
i910 := (P9-P10)/R9; (*flow from pulmonary vein to left atrium*)
i101 := (P10-P1)/R10;   (*flow across mitral valve*)
```

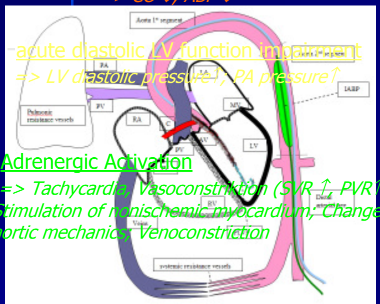
Implantation technique



Pathophysiology of cardiogenic Shock

Basel Heart Disease Simulator
Computational Simulation of heart disease
And cardiovascular therapies

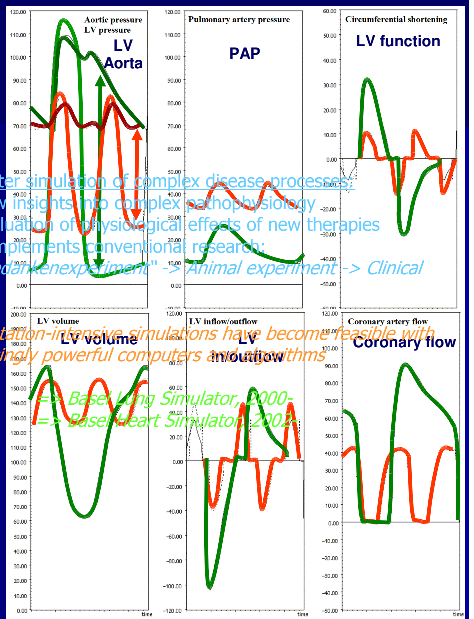
-LV contractility impairment
=> CO ↓, ABP ↓



-acute diastolic LV function impairment
=> LV diastolic pressure↑, PA pressure↑

-Adrenergic Activation
=> Tachycardia, Vasoconstriktion (SVR ↑, PVR↑); Stimulation of nonischemic myocardium; Changes in aortic mechanics; Venoconstriction

Marked reduction of coronary perfusion
<= Tachycardia, ABP ↓, filling pressures ↑ &
- myocardialer O2-consumption ↑ (Catecholamines)

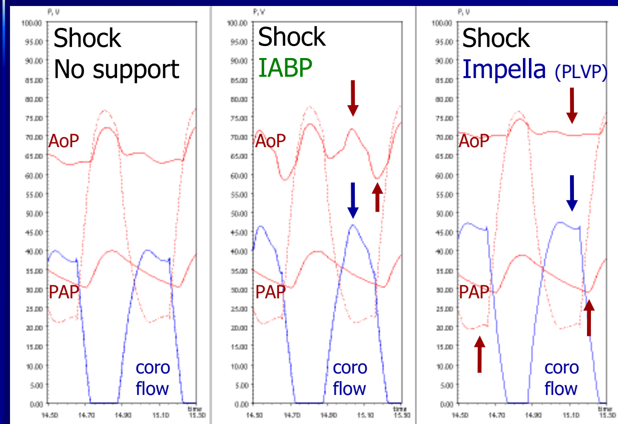


Computer simulation of complex disease processes:
- New insights into complex pathophysiology
- Evaluation of physiological effects of new therapies
- Complements conventional research:
  „Gedankenexperiment" -> Animal experiment -> Clinical trial

Computation-intensive simulations have become feasible with increasingly powerful computers and algorithms

=> Basel Lung Simulator, 2000-
=> Basel Heart Simulator, 2002-

Mechanical support: pressure curves & coronary flow



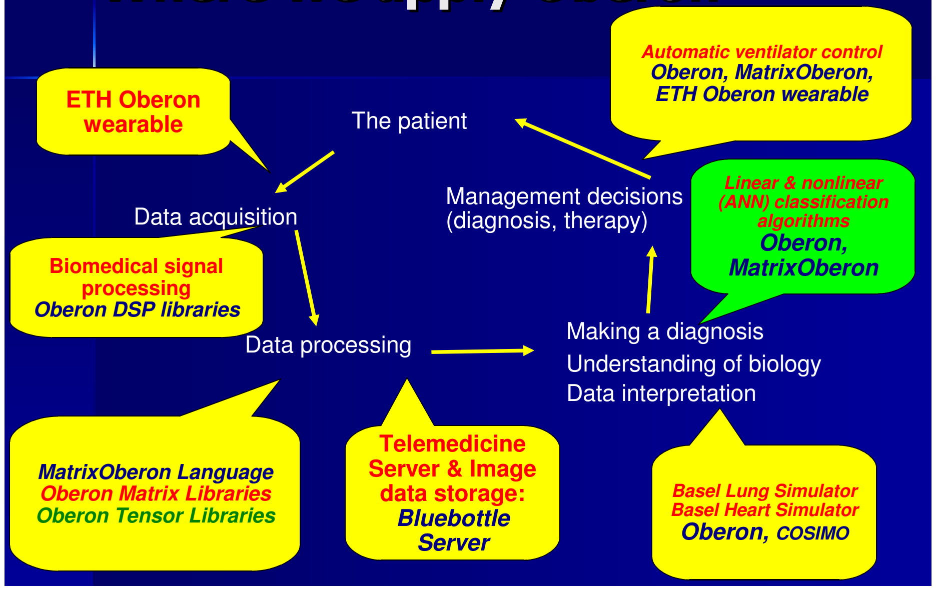
Basel Heart Simulator, Hunziker 2006

Summary

Computational simulation predicts

- Percutaneous LV assist (Impella 2.5) is more effective than IABP for increasing blood pressure and cardiac output, for improving coronary flow, for reduction of cardiac work, and for preload reduction
- Combining percutaneous LV assist with an IABP leads to an added benefit compared to either device alone.
- Of particular hemodynamic promise is the combination of mechanical support modalities with vasodilators
- Percutaneous LV assist is effective in complications which are not helped by IABP support, namely severe arrythmia and profound LV pump failure

Where we apply Oberon



Unsupervised image classification of echo images by automatic "elastic warping".

Schlomo V. Aschkenasy & Patrick Hunziker

Automatic image classification: An example

Sample | Reference | automatic fitted sample | sample & difference

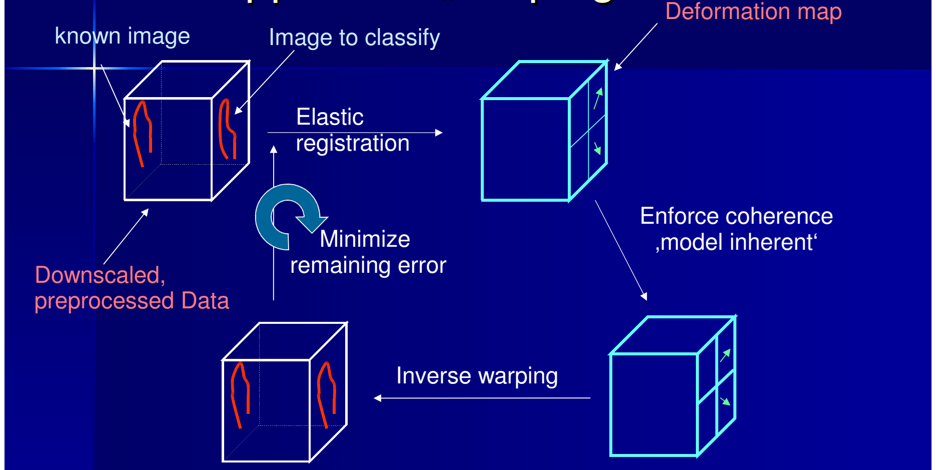
How can we classify medical images ?

- Optical flow equation

$$\delta I/\delta x + \delta I/\delta y + \delta I/\delta t = 0$$

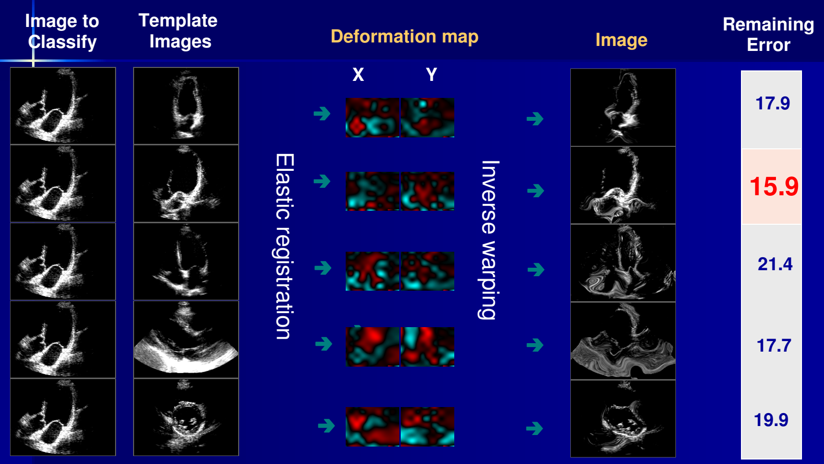
with I: Intensity field I = f(x,y,t)
(i.e., "*objects do not disappear when they move*")

The Approach: „warping“

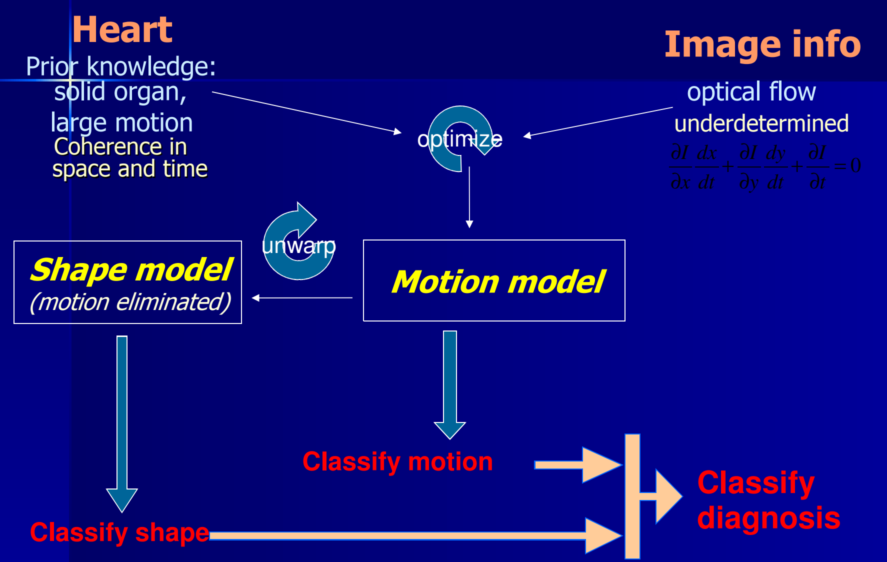


Find a warping map (3D model) that minimizes the difference between a sample and a given template within smoothness constraints.

The Results (shape classification)



The Approach: warping/registration



Results: Classification by view

Linear discriminant analysis

Predicted Image Type					
	Class	**Apex**	**LAX**	**SAX**	**Total**
Original	**Apex**	***45***	2	2	49
	LAX	0	***24***	0	24
	SAX	2	0	***15***	17
Cross-validated	**Apex**	***44***	2	3	49
	LAX	0	***24***	0	24
	SAX	4	0	***13***	17

Original: 93% (Chi2=123.8, $p < .0001$)
'leave-one-out': 90% (Chi2=131.1, $p < .0001$)

Conclusion

- A multiscale elastic registration algorithm implemented in Oberon allows the separation of shape and motion in moving datasets.
- Separating shape and motion is the basis for an automatic classification of echocardiographic images and autonomous computer vision diagnosis.
- Fast, compact code libraries make these algorithms suitable for clinical use in very large datasets.

Summary

- Oberon has proven useful for a broad spectrum of medical applications in a clinical context.
- It has been successfully applied in the fields of
  - Digital signal processing
  - Linear and multilinear algebra application
  - Image processing/analysis
  - Medical Simulation
  - Productive Telemedicine System
  - High Performance Computing
- Of particular usefulness were its following features
  - Language (simplicity, efficacy, safety, readability, maintainability)
  - Matrix language extension
  - Bluebottle server: stability, no virus threat