THE FUTURE of DECISION SUPPORT

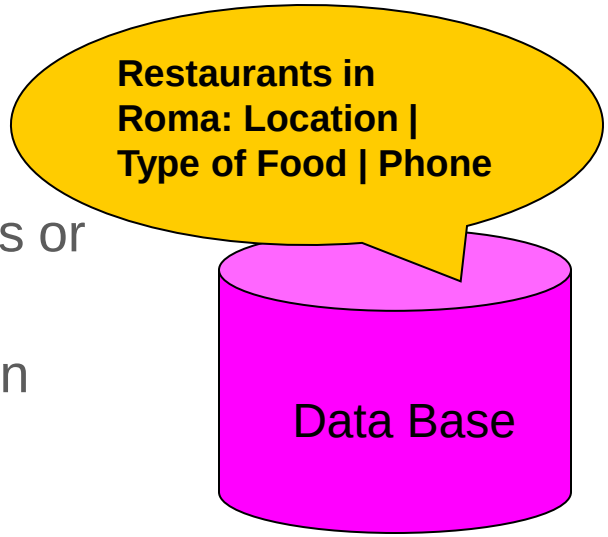
Prof. Giacomo Pongiglione, M.D, F.A.C.C.
Dept. of Pediatric Cardiology and Cardiac Surgery
Bambino Gesù Children's Hospital
Roma, Italy

Bambino Gesù
OSPEDALE PEDIATRICO

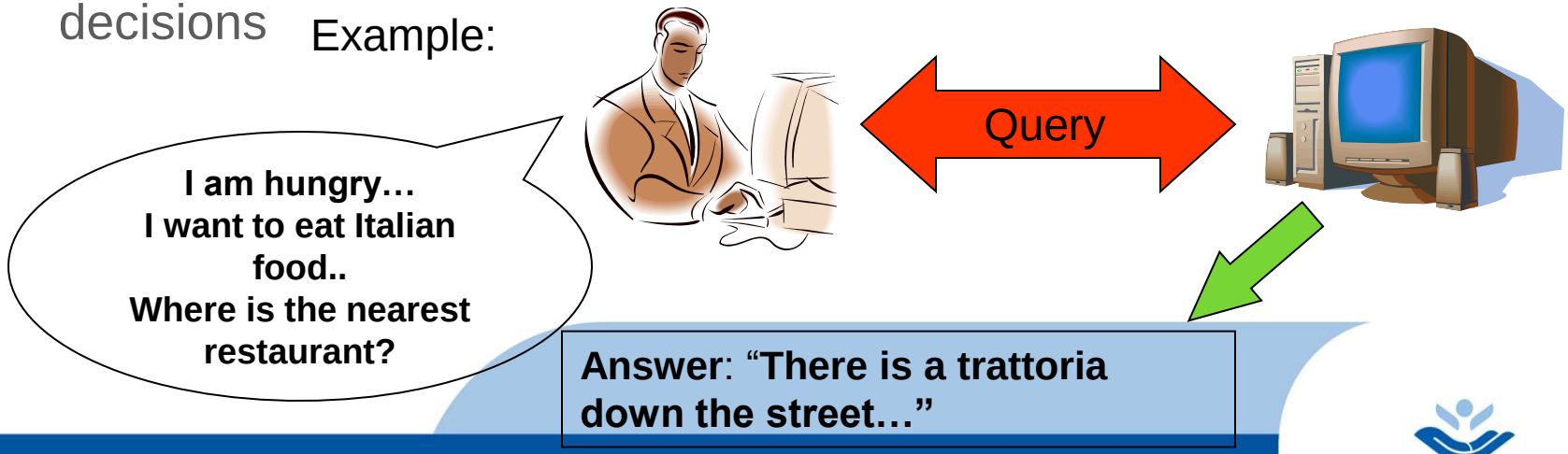
Predictive medicine is a field of medicine that entails predicting the probability of disease and **instituting preventive measures in order to either prevent the disease altogether or significantly decrease its impact upon the patient (such as by preventing mortality or limiting morbidity).** While different prediction methodologies exist, such as genomics, proteomics, and cytomics, the most fundamental way to predict future disease is based on genetics

Data Base

- **Data Base**: A structured collection of records or data that is stored in a computer system
- **Purpose**: A computer program or person can consult it to answer queries
- **How**: Using a query language!!
- **Why**: The records retrieved as answers to queries represent information that can be used to make decisions



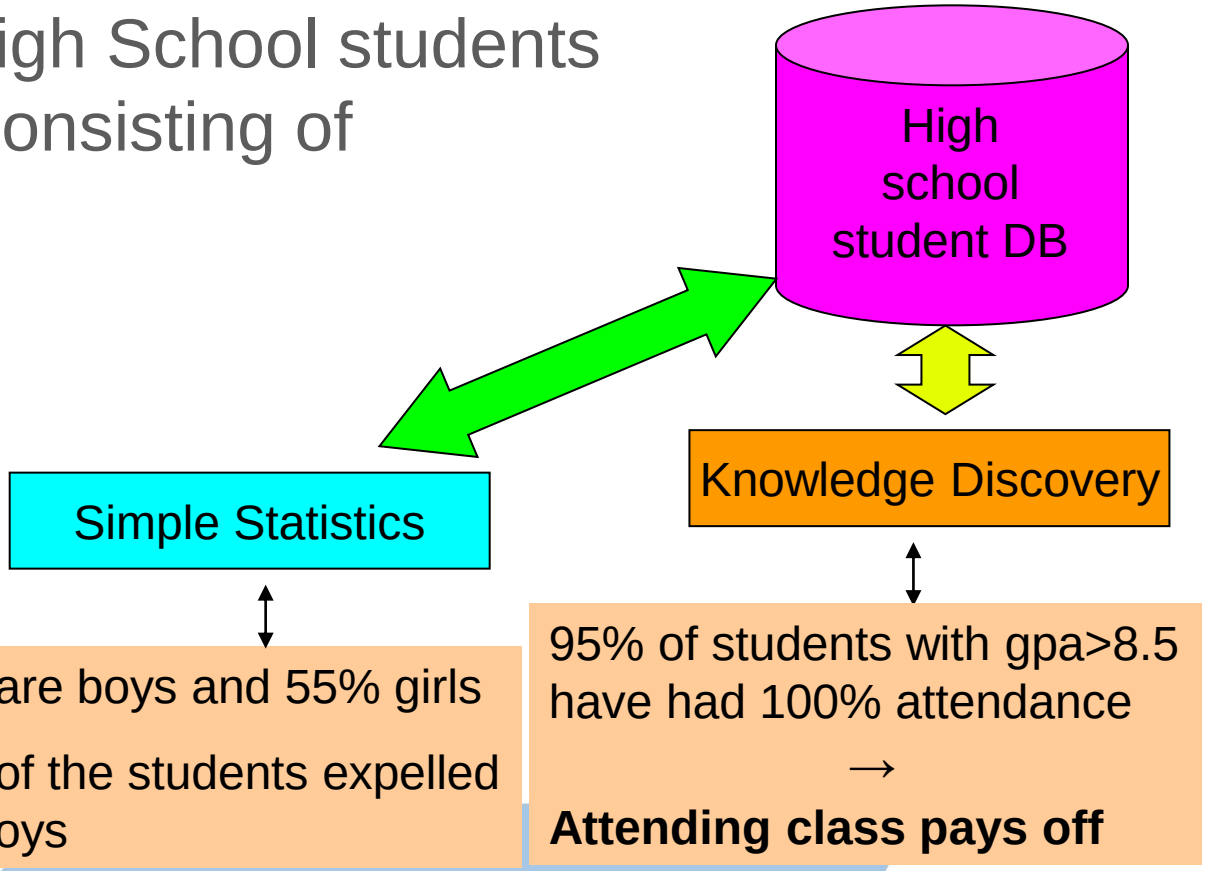
Example:



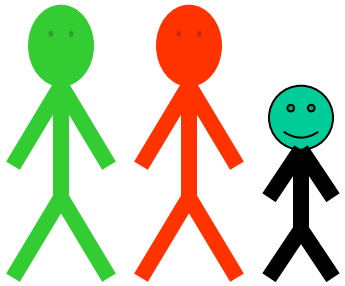
Bambino Gesù
OSPEDALE PEDIATRICO

Knowledge Discovery in Databases

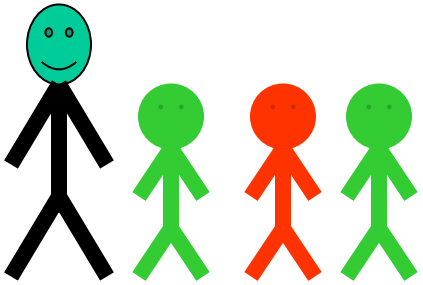
- Database of High School students
- Data records consisting of
  - Age
  - Gender
  - Grades
  - Courses
  - Attendances
  - Behavior
  - …



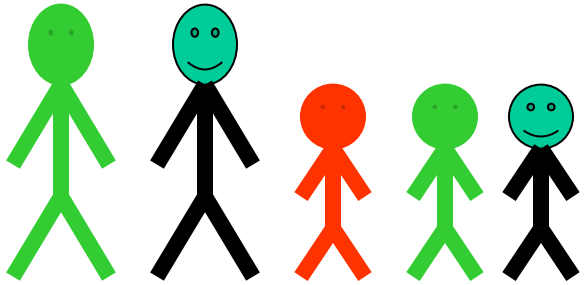
Knowledge Discovery in Medical Databases



London

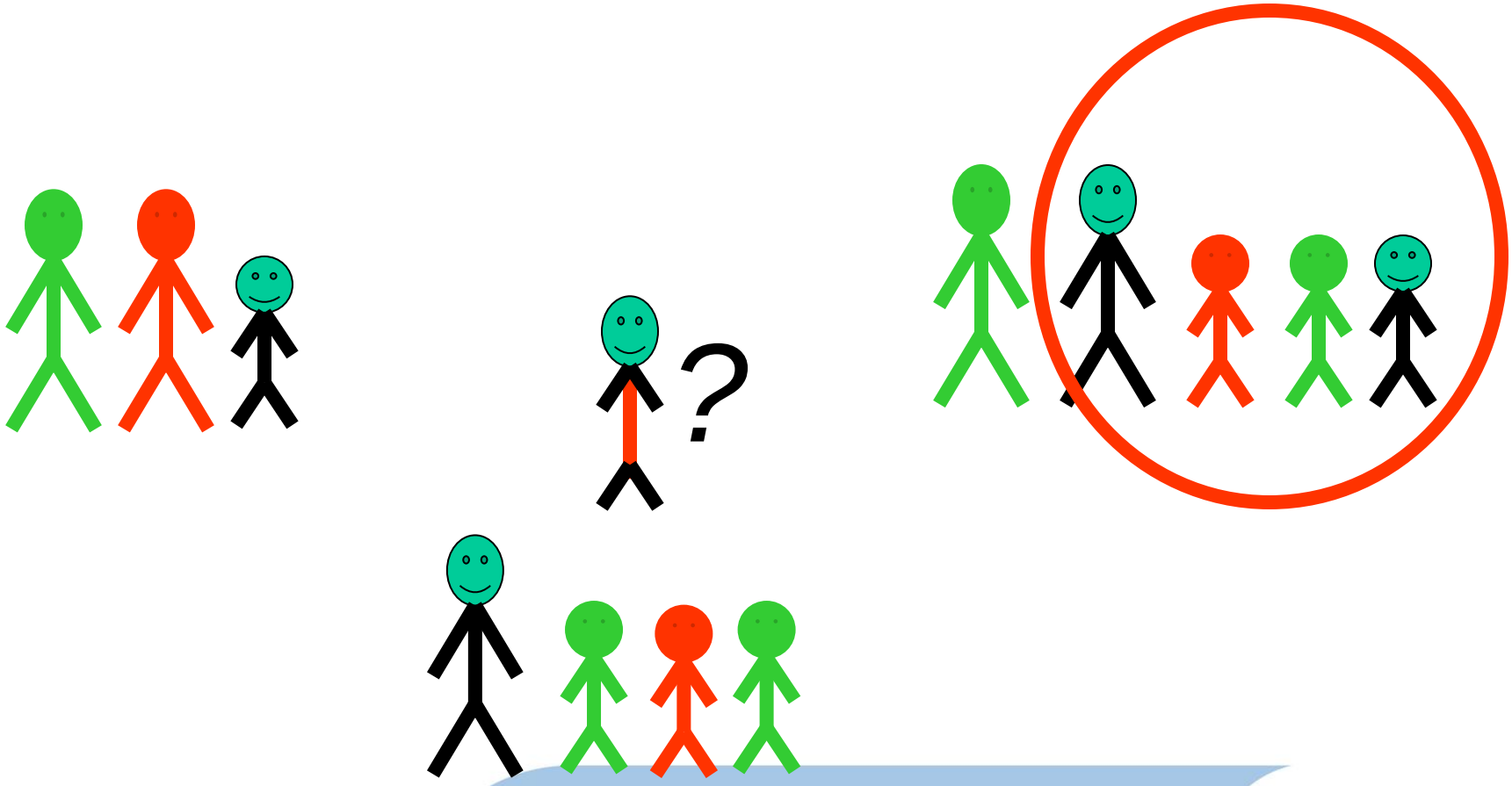


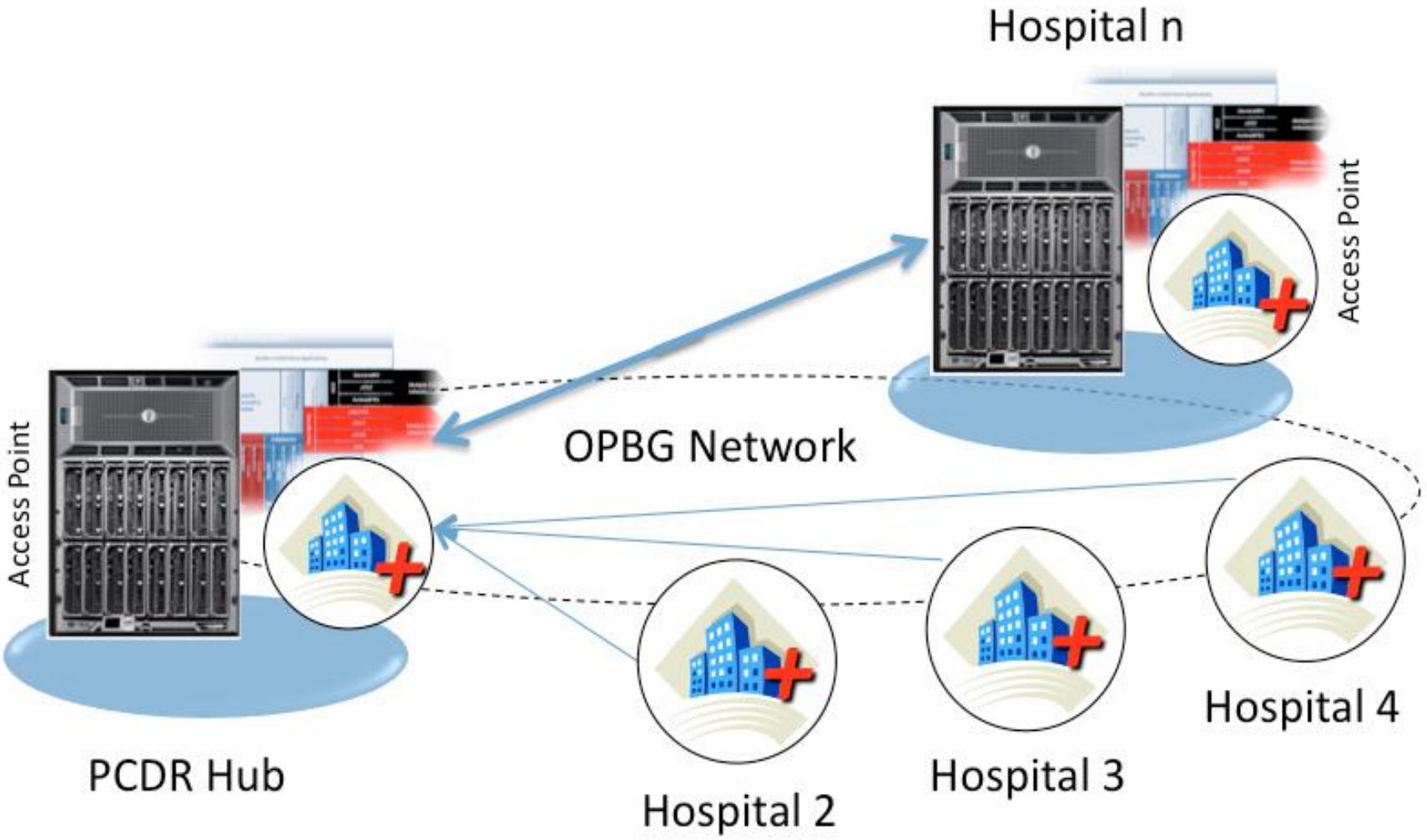
Paris



Roma

Knowledge Discovery in Medical Databases





Bambino Gesù
OSPEDALE PEDIATRICO

Issues and Challenges

Unique features of biomedical data

- Heterogeneous, distributed, and complex data
- High dimensionality (especially in Genomics/Proteomics)
- Lack of standardisation
- Changing data and knowledge (Temporal Evolution)
- Biomedical data not characterized mathematically
- Missing, inconsistent, and noisy data
- Ambiguous result interpretation
- Data ownership, privacy, and security concerns

looking for needles in a genomic haystack

- A common defective genomic region may be related to different phenotypes
- A single phenotype may be related to different gene abnormalities
- Genes with differential expression may indicate a molecular basis for disease development

INTEGRATED DISEASE MODELING

DATA MINING

Identify the distinctive characteristics of each feature

which are the right features?

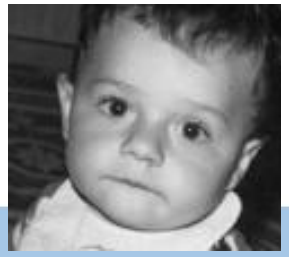
- we have two groups of people we can look at
- we know they can be distinguished for some features but we don't know which

group 1: john charlie steve



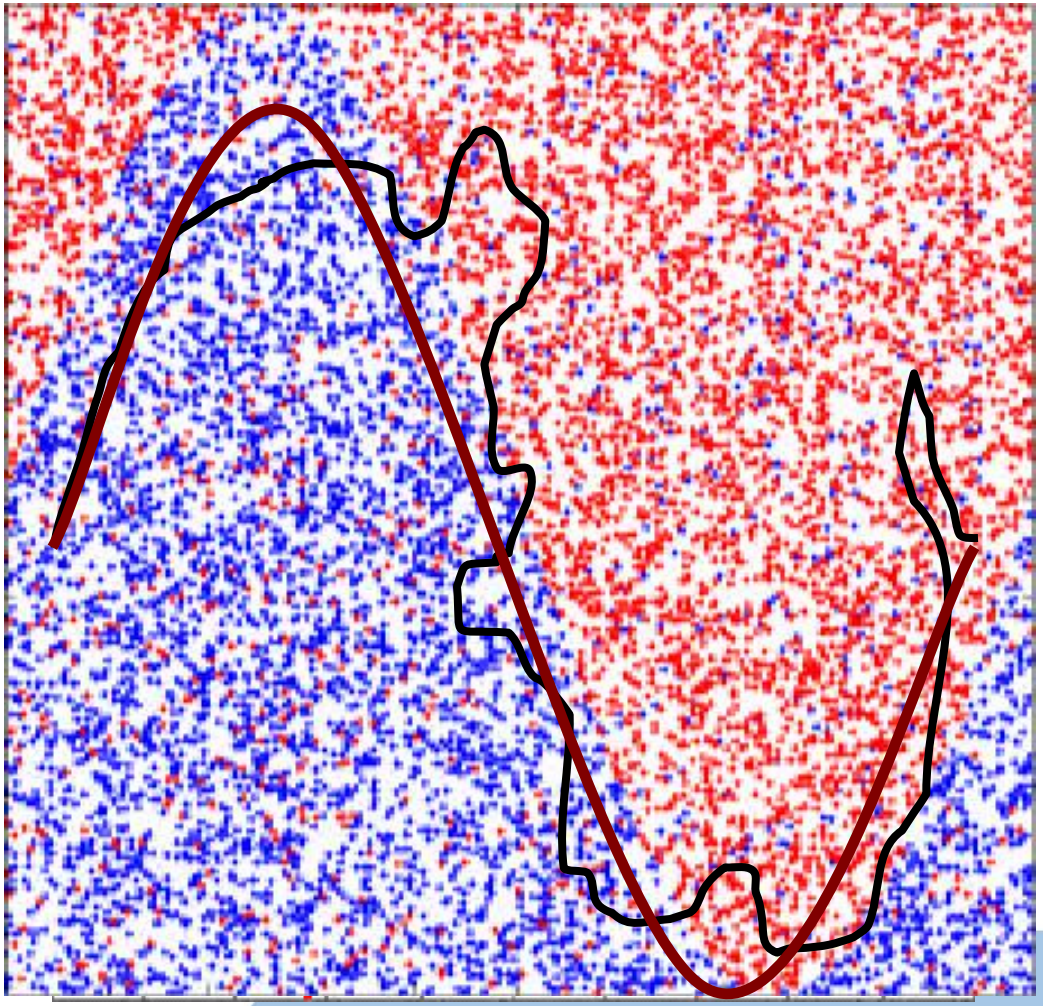
group 2: alice camilla paola





- **Detection theory**, or **signal detection theory**, is a means to quantify the ability to discern between information-bearing energy patterns (called stimulus in humans, signal in machines) and random energy patterns that distract from the information (called noise, consisting of background stimuli and random activity of the detection machine and of the nervous system of the operator).

if dimensions were only two…



what are the right features?

- what if the features are as many as 30000?
- If the feature number is about 30 the number of possible combinations is about

1.000.000.000.000.000.000.000.000.000.000.000.
000.000.000.000.000.000.000.000.000.000.000.
000.000.000.000.000.000.000.000.000.000.000.
000.000.000.000.000.000.000

a cloud consisting of a billion of computers a billion times faster than the fastest existing computer today and working for a billion of years in a billion of planets won’t even scratch the surface of the problem

Unprecedented complexity and diversity of data sets that should be analyzed jointly.

INFORMATION TECHNOLOGY

The future is not what it used to be

Yogi Berra

Information Technology

Read and analyze data through an innovative system of distributed computation (CLOUD)

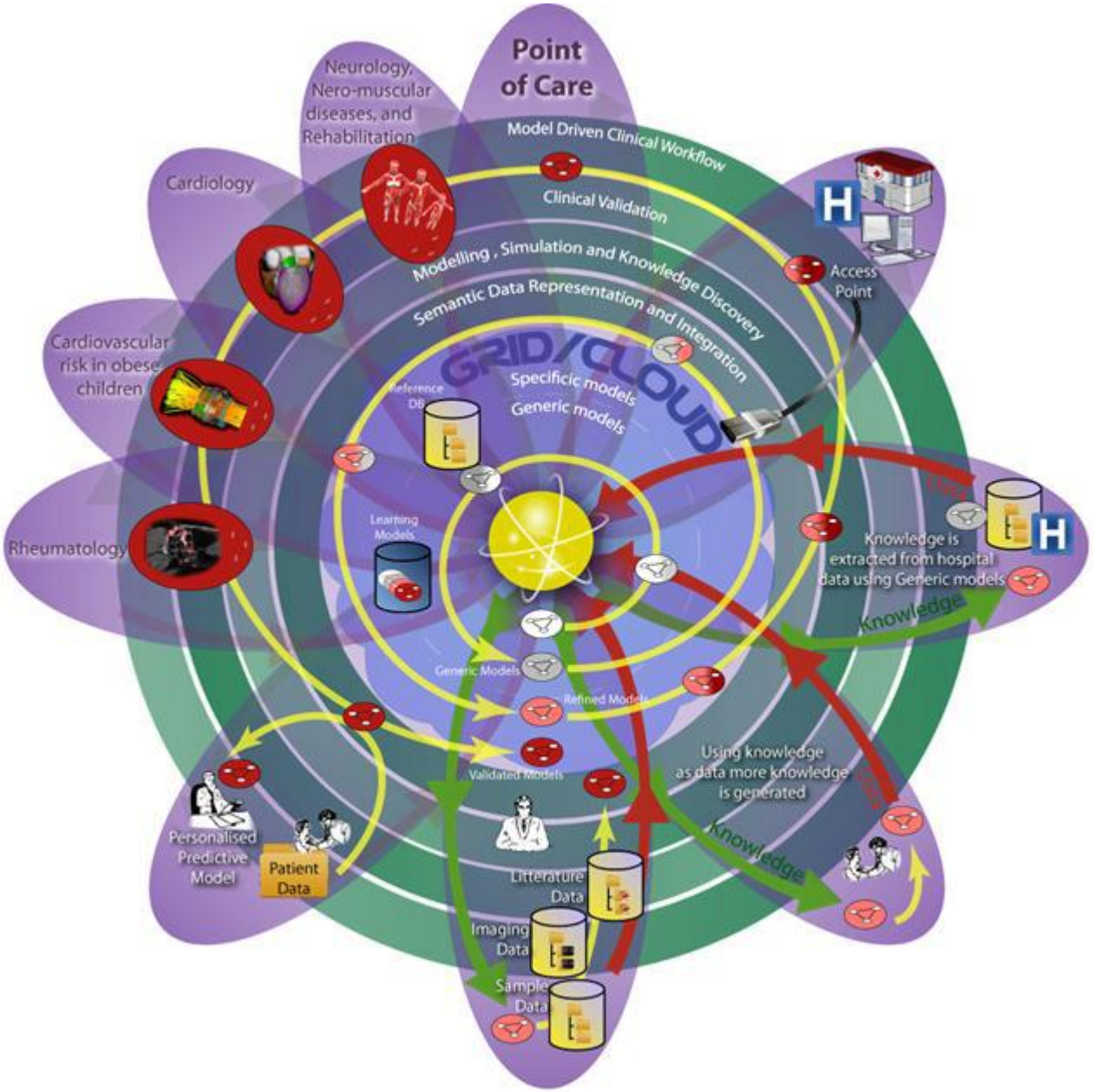
Network

- Connectivity
- Security
- Computational power

- **IaaS** Infrastructure as a Service (Repository, Xcelera, XDS,…)
- **PaaS** Platform as a Service (Cloud applications)
- **SaaS** Software as a Service (…)
- **MaaS** Model as a Service

- VPH projects need high quality data sets based on significant amounts of routine data

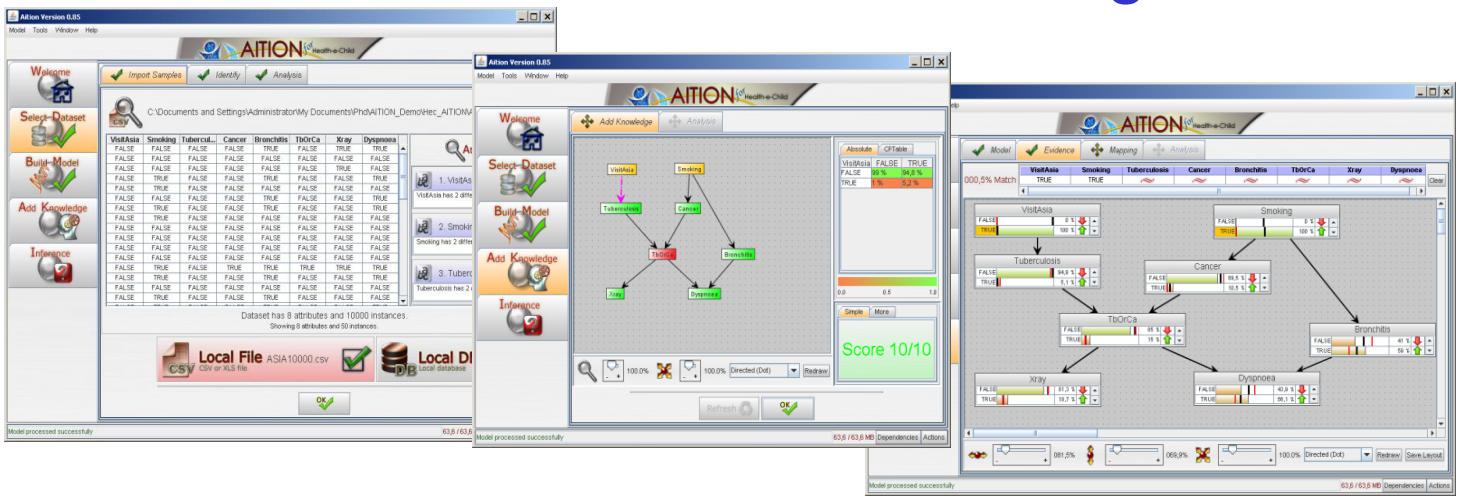
SOKU



Bambino Gesù
OSPEDALE PEDIATRICO

KDD Platform

A comprehensive information processing and knowledge discovery framework based on (non parametric) Bayesian data analysis & Graphical Probabilistic Modelling



Bambino Gesù
OSPEDALE PEDIATRICO

KDD Platform

Is able to provide highly accurate predictive and simulation models by:

- analyzing heterogeneous, structured and uncertain data. **Data curation** (missing data, inconsistent, outliers) **(bottom up data driven process)**
- incorporating external knowledge coming from domain experts, literature, and relational / semantic models **(top down model/concept driven process)**

Model Guided Personalized Medicine

a-priori-knowledge

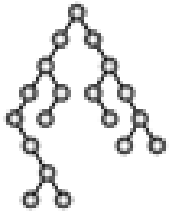
Causal Feature Selection

(Markov Blanket Induction)

Significant Features

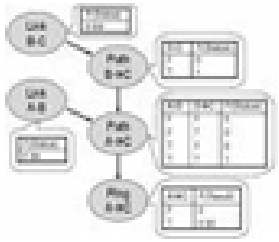
Var1		VarN

Observations



Ontologies

BN Learning (structure and Joint Probability Distributions)

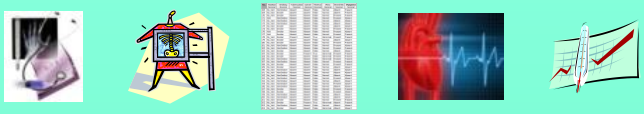


(Causal) Bayesian Network

Ontology-Driven Uncertainty modelling

Bambino Gesù
OSPEDALE PEDIATRICO

Model Guided Personalized Medicine



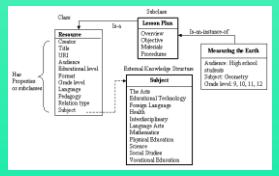
Raw data from biomarker based personalized acquisition

Domain knowledge & assumptions

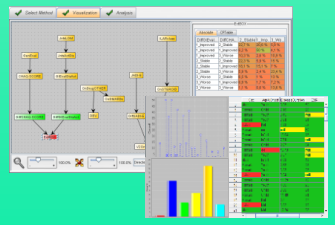
Clinical workflows

Data Acquisition → **Data Analysis** → **Patient specific modeling** → **Personalized Model Guided Medicine**

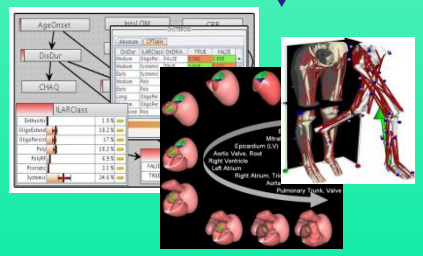
Provenance & model | Knowledge Discovery | Model and verification | Inference and decision support



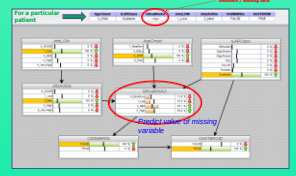
Semantic Model



Information constructs

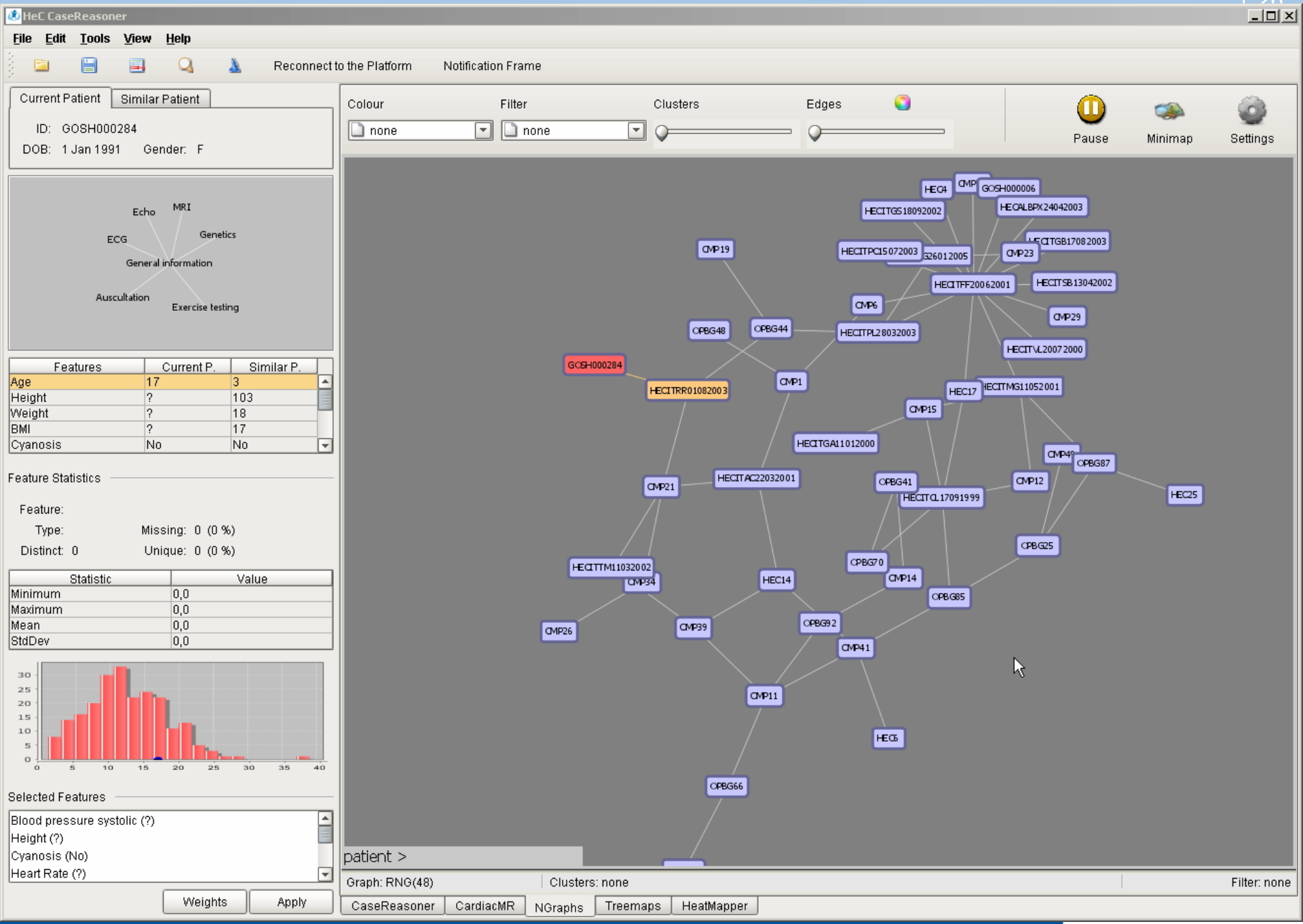


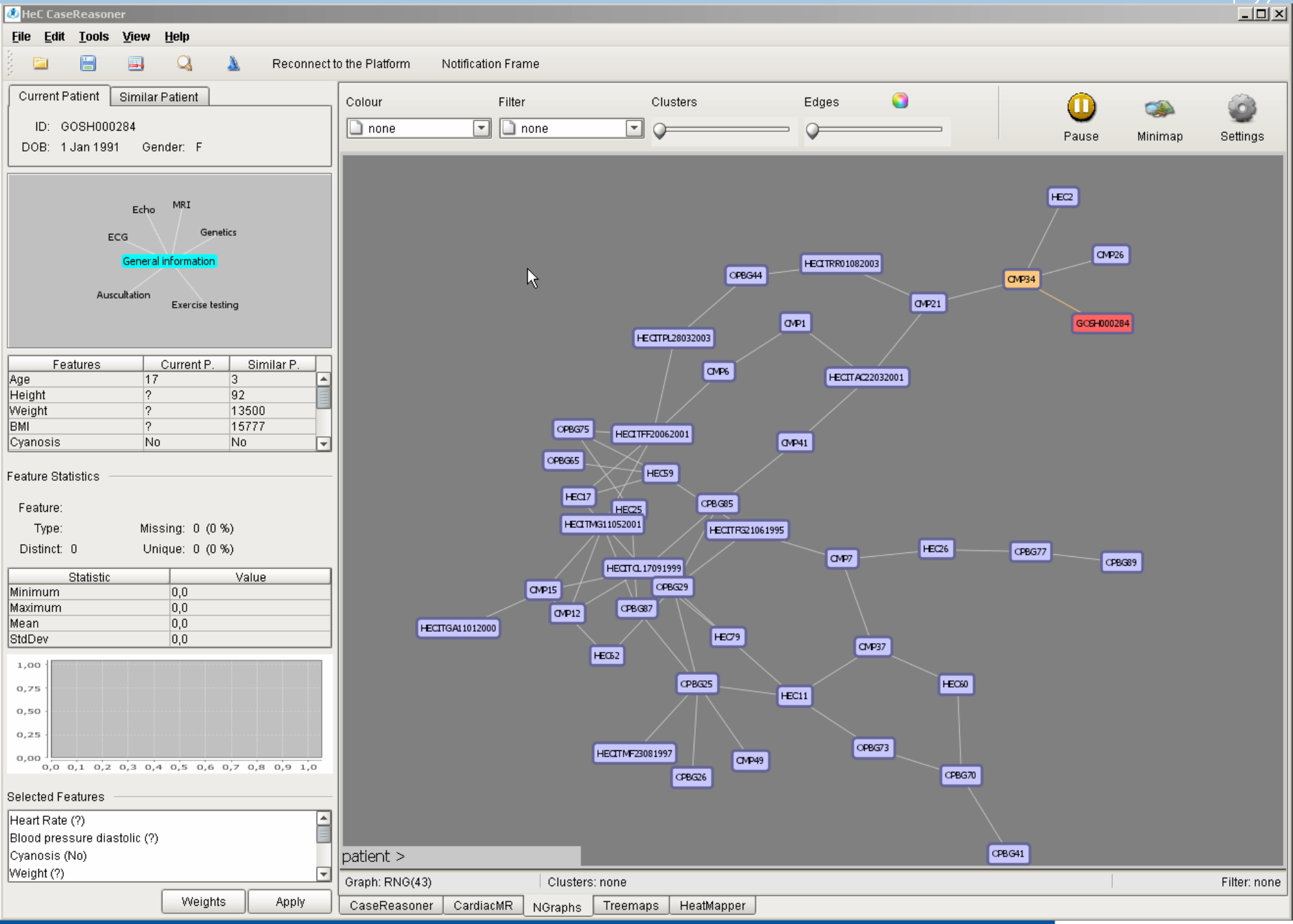
Simulation Models & Patient profiles



Individualized diagnosis, prognosis and treatment plan

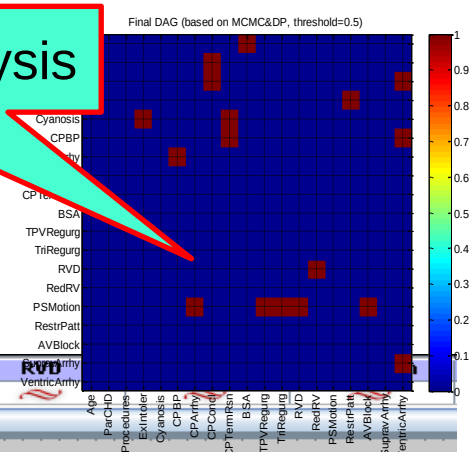
Bambino Gesù
OSPEDALE PEDIATRICO

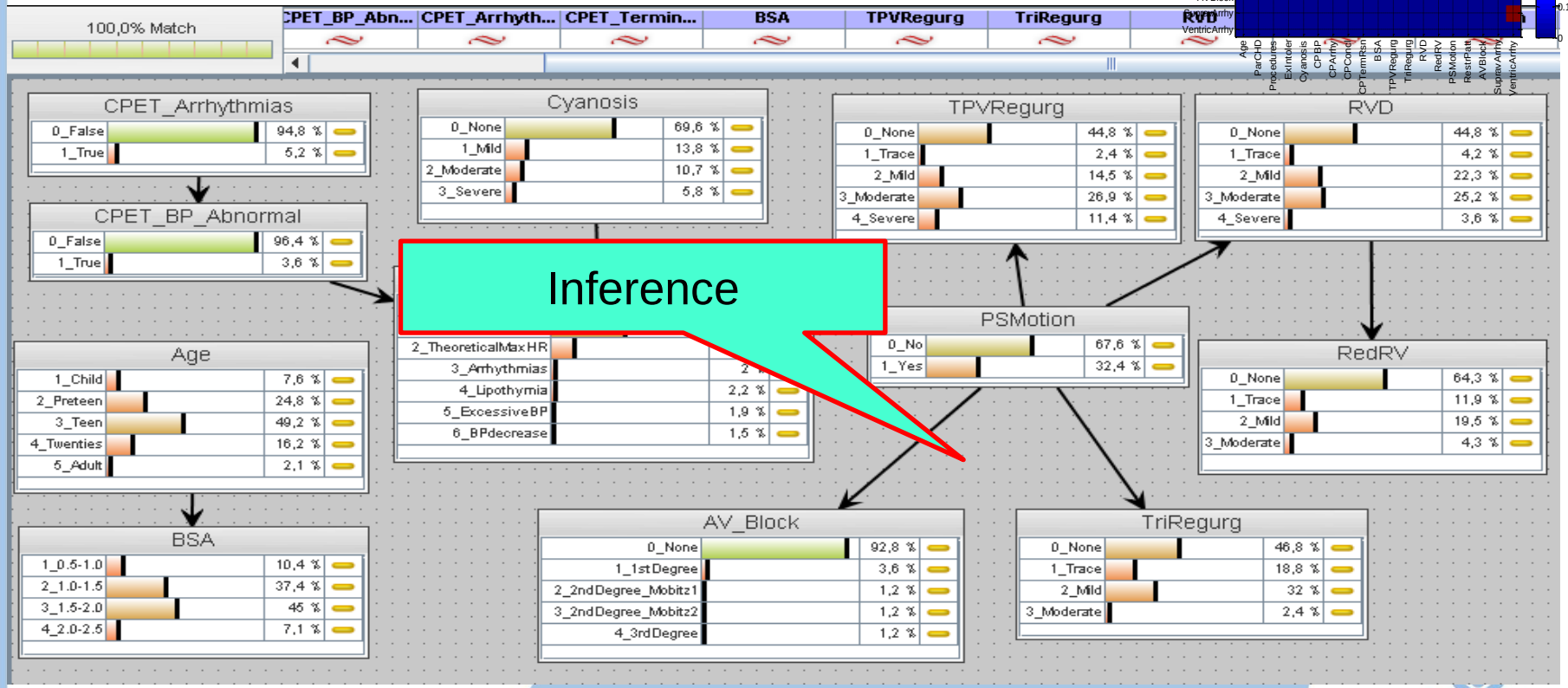

HeC CaseReasoner
File Edit Tools View Help
Reconnect to the Platform
Notification Frame
Current Patient
Similar Patient
ID: GOSH000284
DOB: 1 Jan 1991 Gender: F
Echo
MRI
ECG
Genetics
General information
Auscultation
Exercise testing
Features | Current P. | Similar P.
Age | 17 | 3
Height | ? | 103
Weight | ? | 18
BMI | ? | 17
Cyanosis | No | No
Feature Statistics
Feature:
Type:
Missing: 0 (0 %)
Distinct: 0
Unique: 0 (0 %)
Statistic | Value
Minimum | 0,0
Maximum | 0,0
Mean | 0,0
StdDev | 0,0
Selected Features
Blood pressure systolic (?)
Height (?)
Cyanosis (No)
Heart Rate (?)
Weights
Apply
Colour
Filter
Clusters
Edges
Pause
Minimap
Settings
none
none
GOSH000284
HECITRR01082003
CMP1
CMP19
OPBG48
OPBG44
HECITPL28032003
HECITPC15072003
CMP23
HECITFF20062001
HECITSB13042002
CMP6
CMP29
HECITVL20072000
HECITMG11052001
HEC17
CMP15
HECITGA11012000
CMP21
HECITAC22032001
OPBG41
CMP12
HECITCL17091999
HEC25
OPBG87
CMP49
OPBG25
OPBG70
CMP14
HECITTM11032002
CMP34
HEC14
OPBG85
CMP26
CMP39
OPBG92
CMP41
CMP11
HEC5
OPBG66
patient >
Graph: RNG(48)
Clusters: none
Filter: none
CaseReasoner
CardiacMR
NGraphs
Treemaps
HeatMapper


HeC CaseReasoner
File Edit Tools View Help
Reconnect to the Platform
Notification Frame
Current Patient
Similar Patient
ID: GOSH000284
DOB: 1 Jan 1991 Gender: F
Echo
MRI
ECG
Genetics
General information
Auscultation
Exercise testing
Features | Current P. | Similar P.
Age | 17 | 3
Height | ? | 92
Weight | ? | 13500
BMI | ? | 15777
Cyanosis | No | No
Feature Statistics
Feature:
Type:
Missing: 0 (0 %)
Distinct: 0
Unique: 0 (0 %)
Statistic | Value
Minimum | 0,0
Maximum | 0,0
Mean | 0,0
StdDev | 0,0
1,00
0,75
0,50
0,25
0,00
0,0 0,1 0,2 0,3 0,4 0,5 0,6 0,7 0,8 0,9 1,0
Selected Features
Heart Rate (?)
Blood pressure diastolic (?)
Cyanosis (No)
Weight (?)
Weights
Apply
Colour
Filter
Clusters
Edges
none
none
Pause
Minimap
Settings
HEC2
CMP26
CMP34
HECITRR01082003
OPBG44
CMP21
GOSH000284
CMP1
HECITPL28032003
CMP6
HECITAC22032001
OPBG75
HECITFF20062001
CMP41
OPBG65
HEC59
HEC17
HEC25
OPBG85
HECITMG11052001
HECITFG21061995
CMP7
HEC26
OPBG77
OPBG89
HECITCL17091999
CMP15
OPBG29
CMP12
OPBG87
HECITGA11012000
HEC79
HEC62
CMP37
OPBG25
HEC11
HEC60
HECITMF23081997
CMP49
OPBG73
OPBG26
OPBG70
OPBG41
patient >
Graph: RNG(43)
Clusters: none
Filter: none
CaseReasoner
CardiacMR
NGraphs
Treemaps
HeatMapper

Modelling

Dependency Analysis





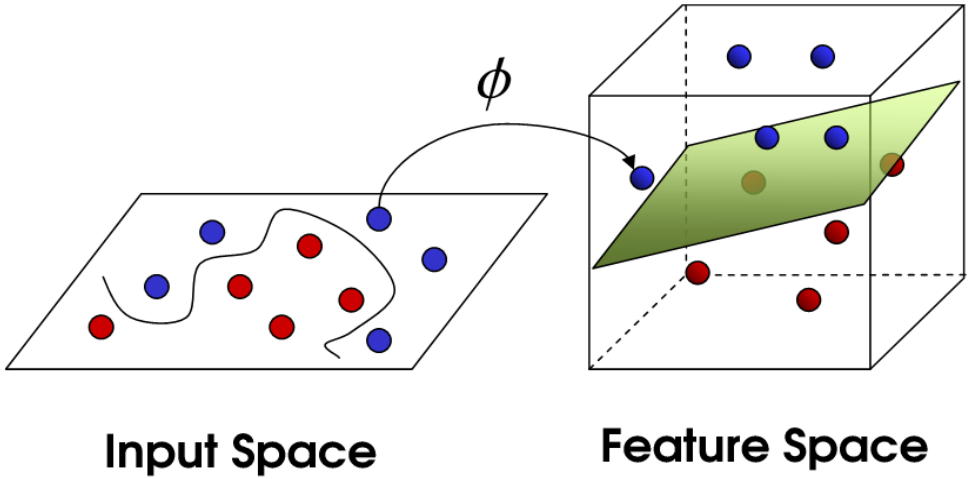
Bambino Gesù
OSPEDALE PEDIATRICO

INFORMATION TECHNOLOGY

Go beyond the classic pair-comparison

Kernel

what is a kernel?



a kernel *K* is an implicit representation of a nonlinear function ϕ mapping input data to a possibly high dimensional feature space in which the original problem can be solved linearly

$$K(x,s) = \langle \phi(x), \phi(s) \rangle$$

Bambino Gesù
OSPEDALE PEDIATRICO

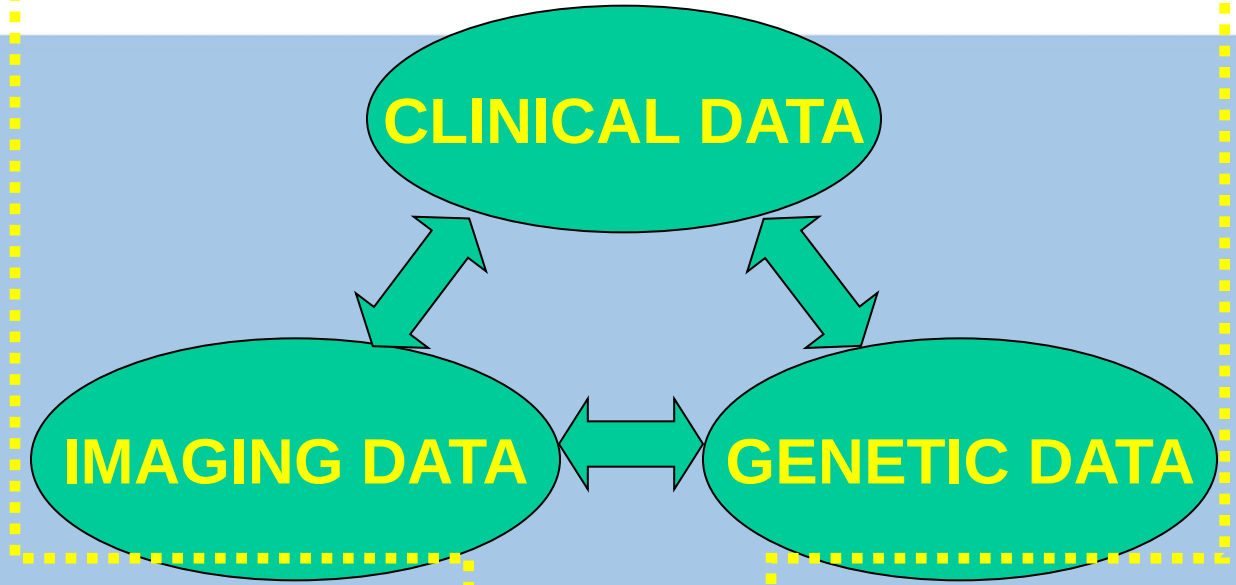
Knowledge Discovery includes

Machine Learning

Visualization

Statistics

Databases



INTEGRATED DATA

Integrated disease modeling

Decision support system

Knowledge discovery

Bambino Gesù
OSPEDALE PEDIATRICO

Disease Modelling

Prof. Giacomo Pongiglione, M.D, F.A.C.C.
Dept. of Pediatric Cardiology and Cardiac Surgery
Bambino Gesù Children's Hospital
Roma, Italy

Bambino Gesù
OSPEDALE PEDIATRICO

MEDICAL DECISION

EPIDEMIOLOGY: Study of the patterns, causes, and effects of a disease in a defined population

DISEASE MODELING

Personalized Medicine is a medical model that proposes the customization of healthcare, with decisions and practices being tailored to the individual patient by use of genetic or other information

DISEASE MODELLING

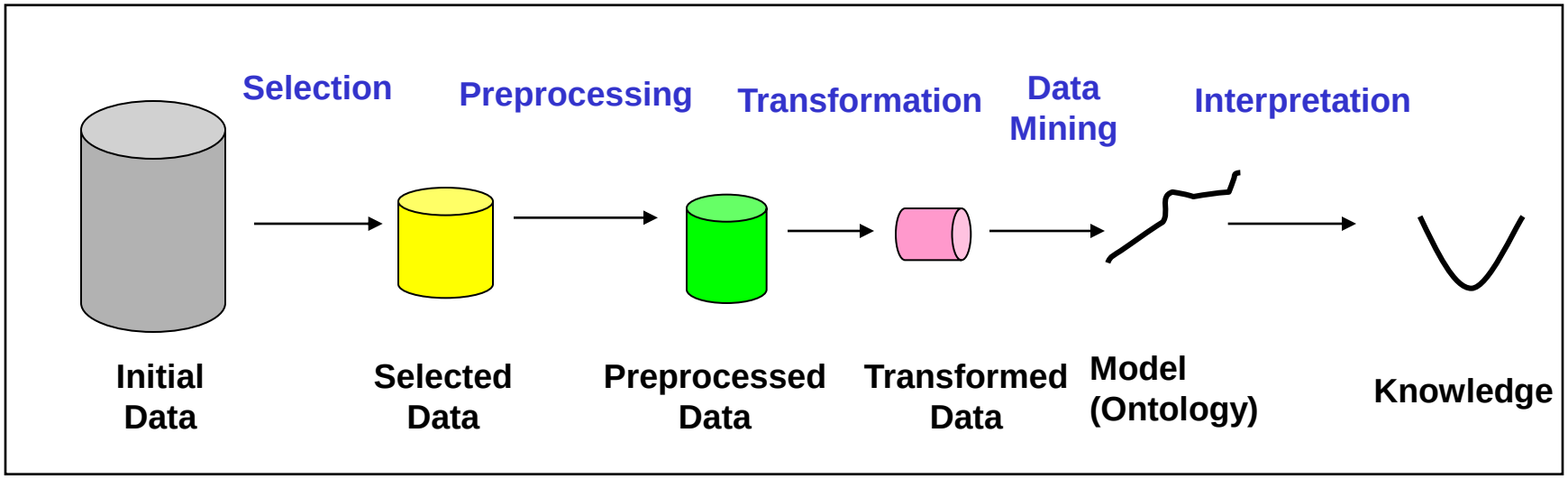
Computational system biology aims to develop and use efficient algorithms, data structures, and visualization with the goal of **computer modelling of biological systems.** It involves the use of computer simulation of biological systems to both analyze and visualize the complex connections of these processes.

what a computer really sees…

221	234	243	255	230	209	213	156	17	20
233	213	224	245	232	201	154	34	34	16
209	233	212	212	212	90	34	44	45	10
205	200	212	245	84	67	65	43	18	9
221	223	203	156	67	64	18	15	13	20
234	223	225	226	60	55	44	15	10	2
190	225	217	236	57	65	145	156	178	153
249	217	204	222	78	75	101	78	144	123
237	234	217	245	73	74	22	90	144	112

Bambino Gesù
OSPEDALE PEDIATRICO

By Applying Knowledge Discovery Processes



INTEGRATED DISEASE MODELING ONTOLOGY

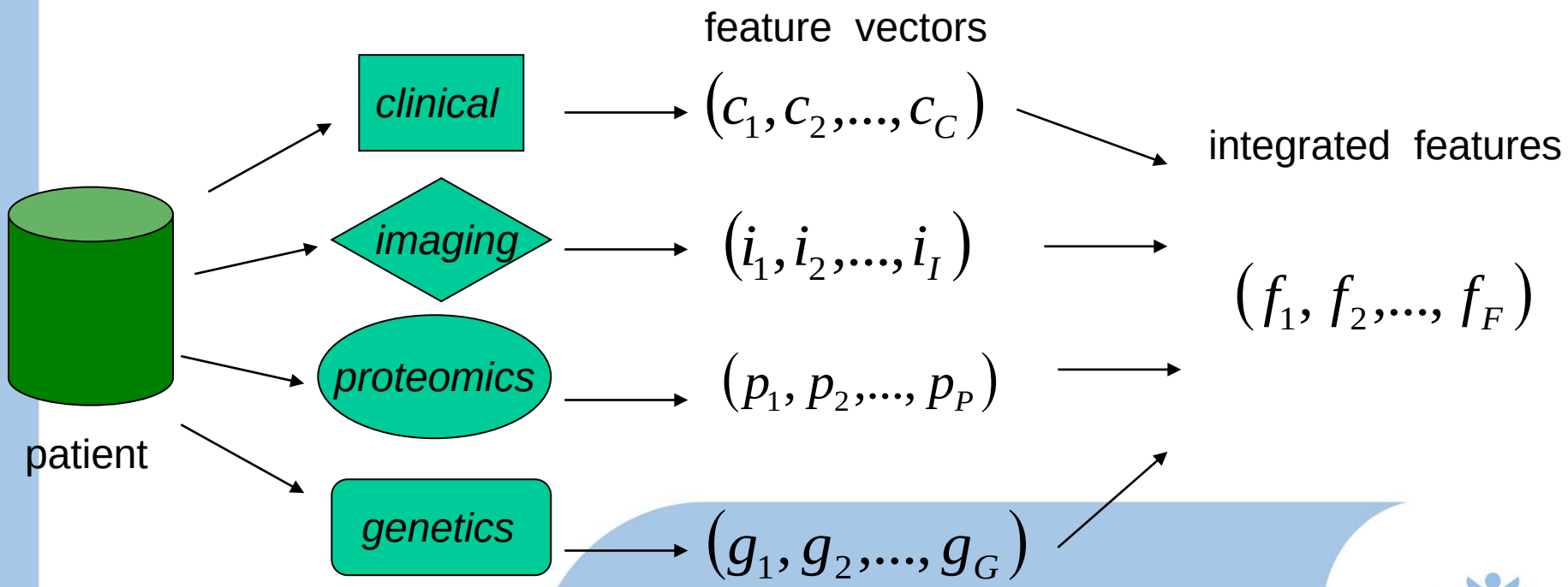
“Specification of a Conceptualization”

Domain of knowledge, represented by facts and their logical connections, structured by formal rules, that can be interpreted and used by computers.

Solomonides T, McClatchey R, Breton V, Legrè Y, Norager S. editors. From Grid to Healthgrid. Proceedings of Healthgrid 2005

A simple approach → Using a single heterogeneous vector

- For each patient, measurements from different data sources are combined into a single feature vector (→ heterogeneous data).



INTEGRATED DISEASE MODELING

ONTOLOGY

Creation of a mathematical model of the disease integrating environmental, familiar, genetic, clinical data, imaging, etc.

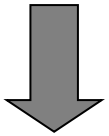
Solomonides T, McClatchey R, Breton V, Legrè Y, Norager S. editors. From Grid to Healthgrid. Proceedings of Healthgrid 2005

Health-e-Child Project

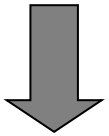
Giacomo Pongiglione - Clinical Coordinator

Department of Pediatric Cardiology and Cardiac Surgery
Ospedale Pediatrico Bambino Gesù. Roma

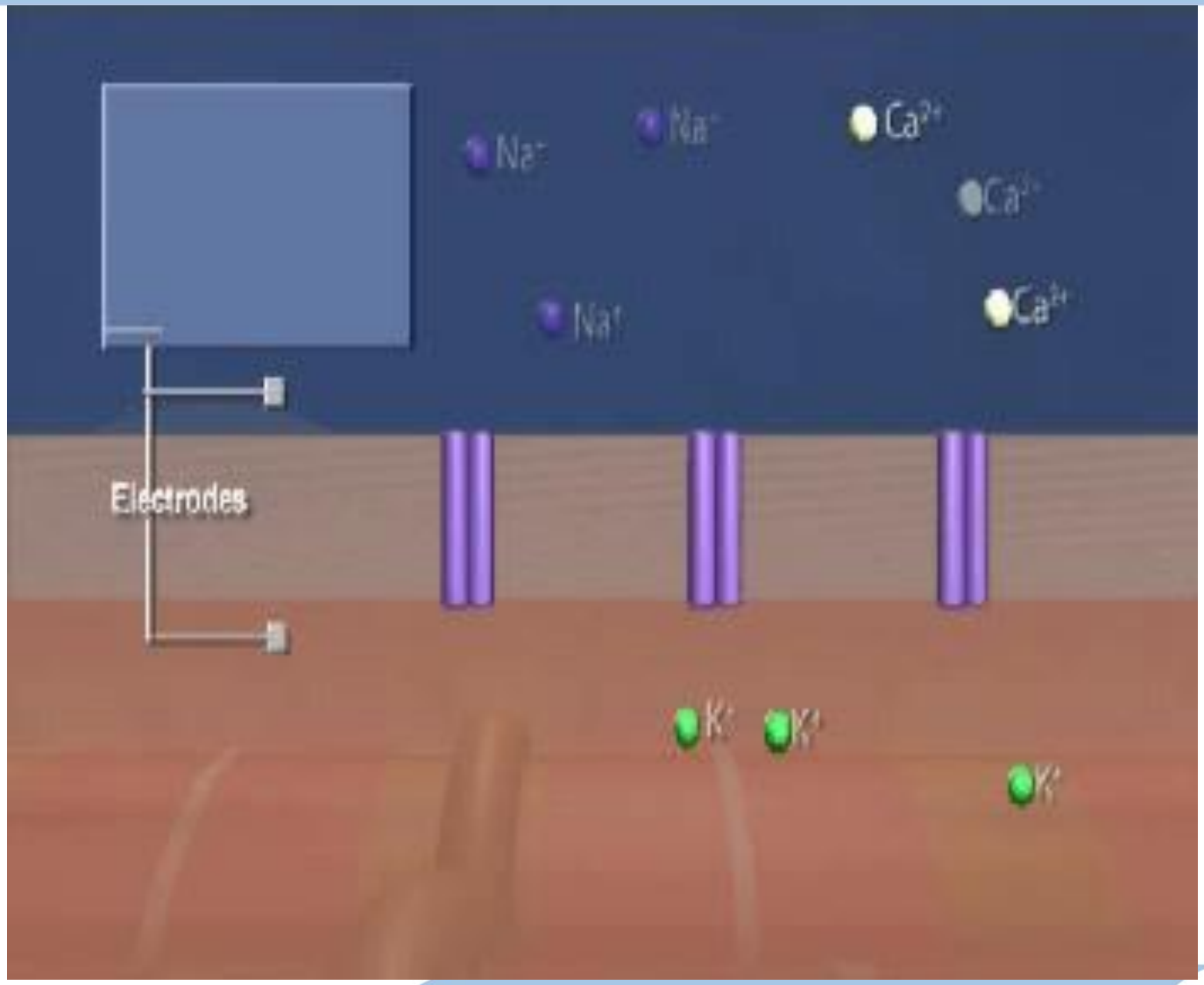
Step 1 – Build a Patient-Specific Anatomical Model from cardiac MRI

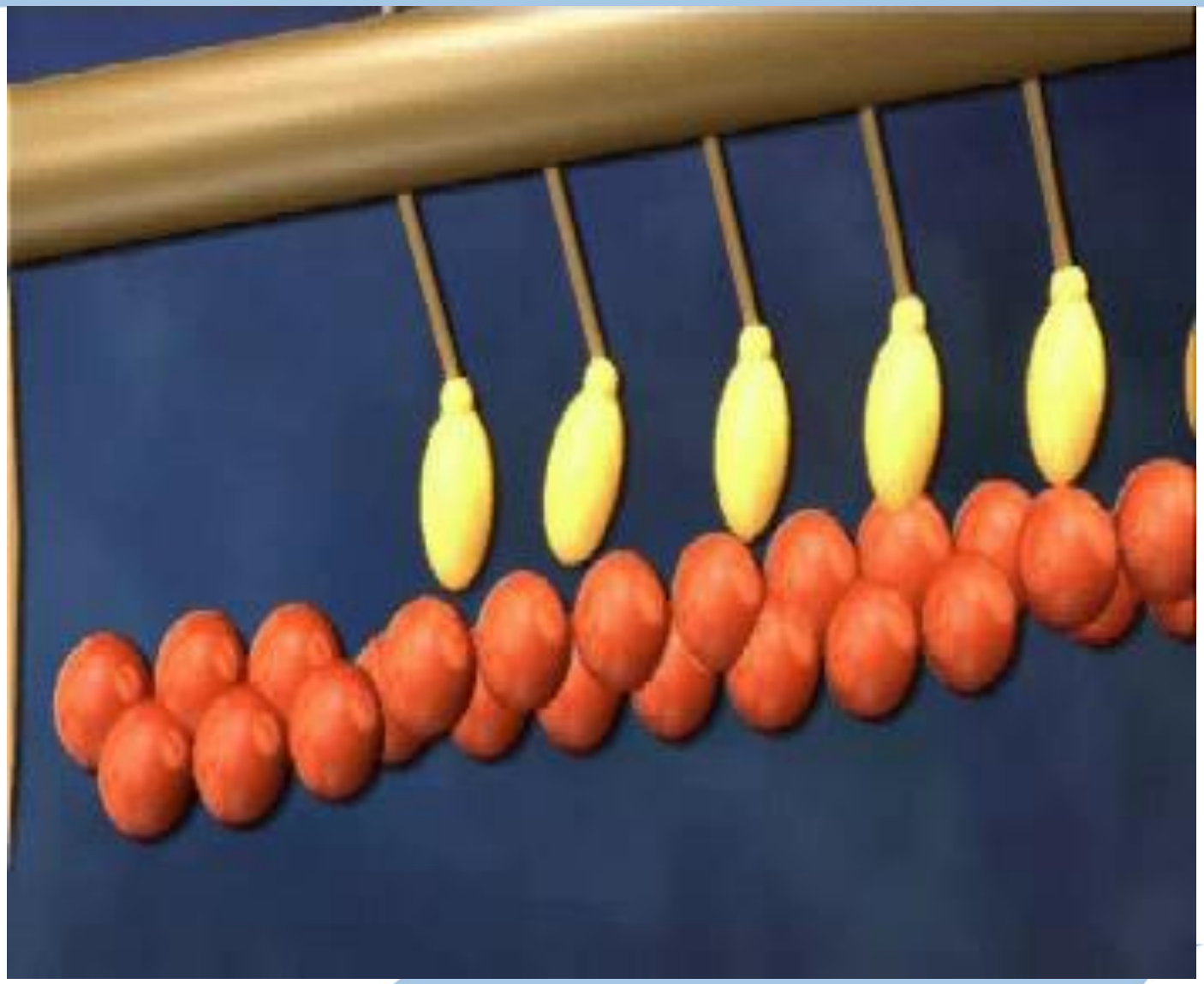


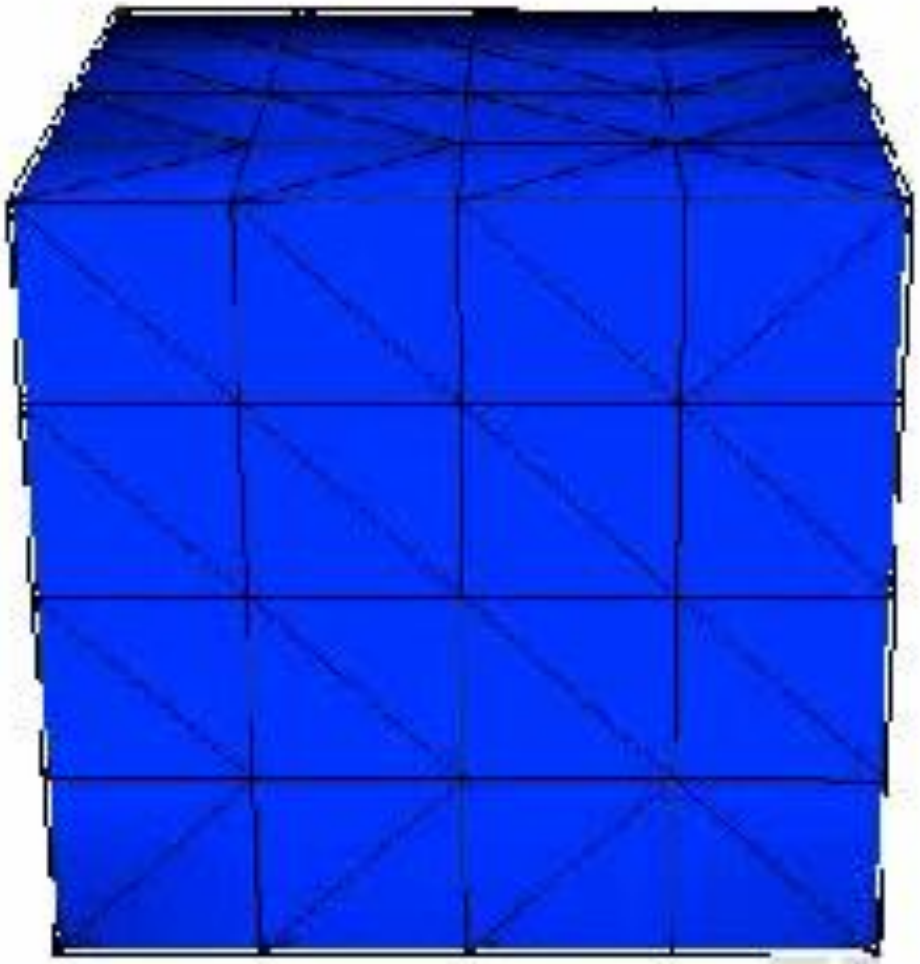
Step 2 – Simulate Patient Cardiac Function using an Electromechanical Model of the Heart

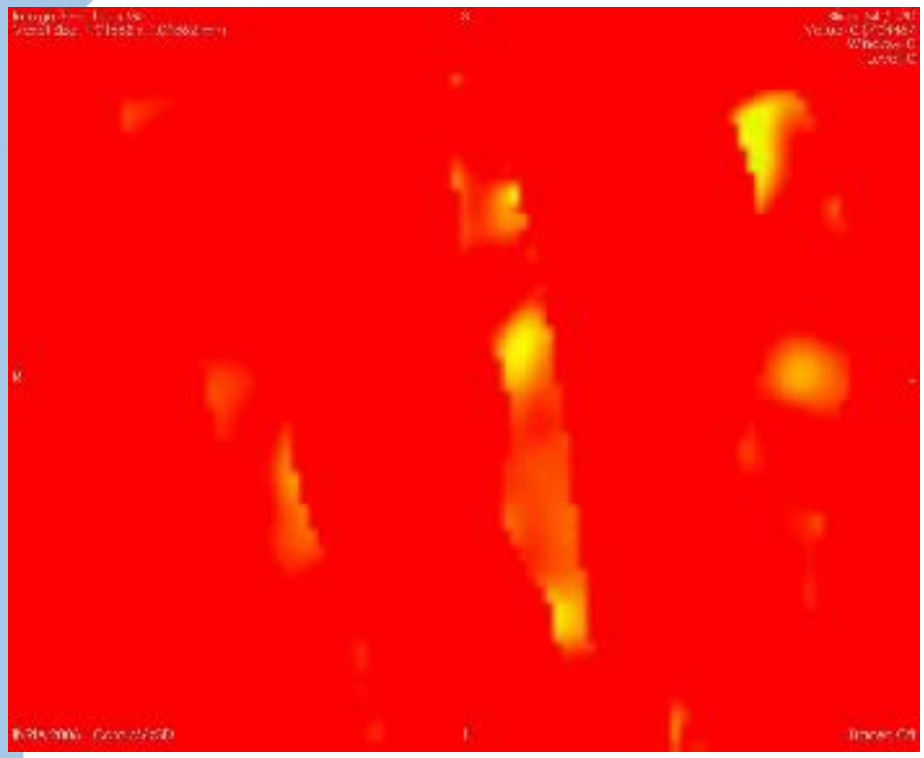


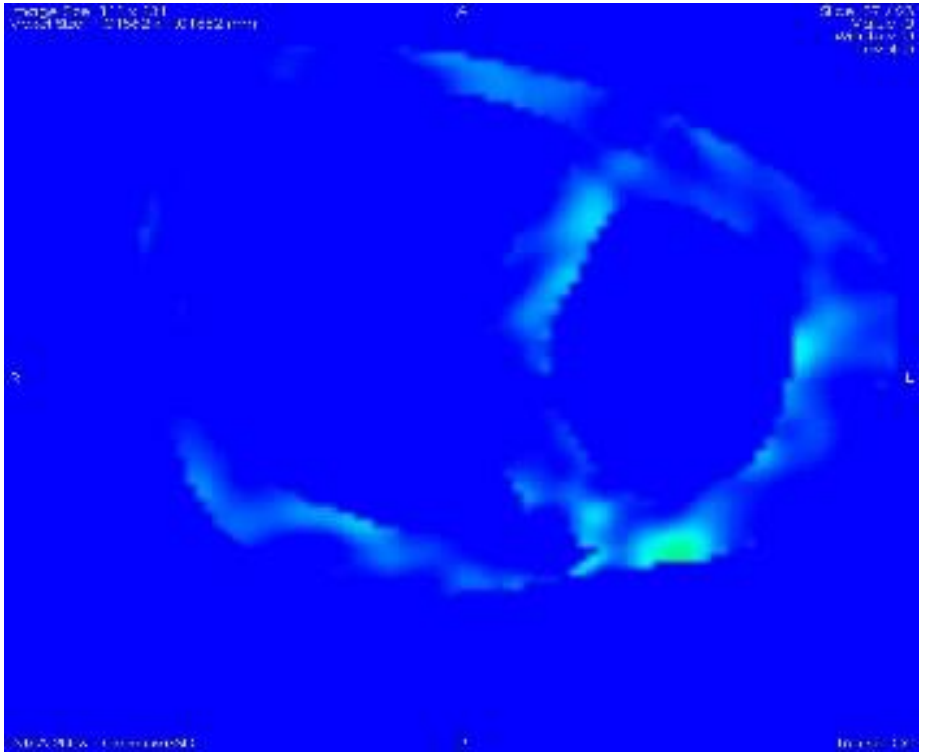
Step 3 – Simulate PVR Therapies using Soft-Tissue Intervention Platform

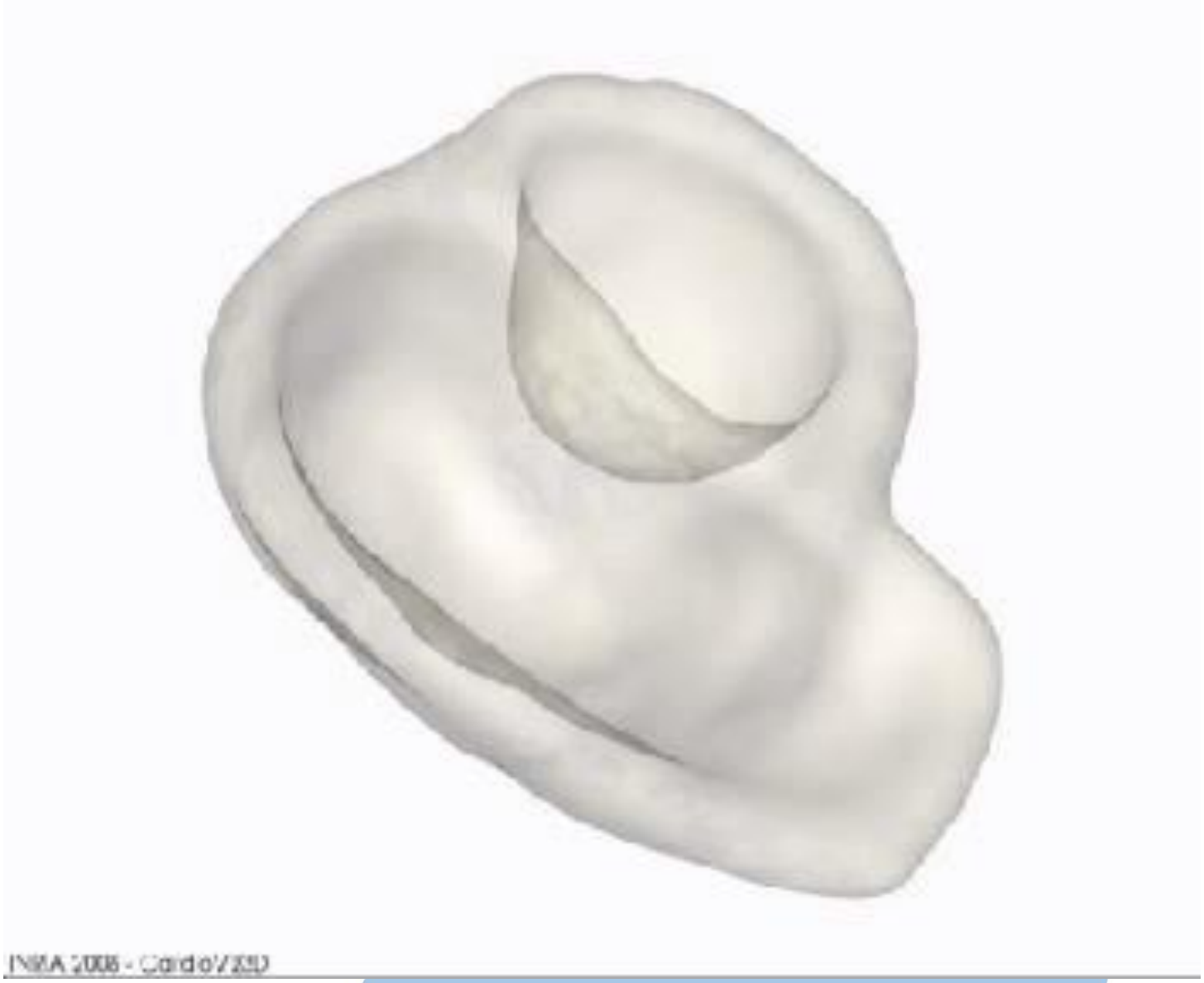

Na+
Na+
Ca2+
Ca2+
Na+
Ca2+
Electrodes
K+
K+
K+





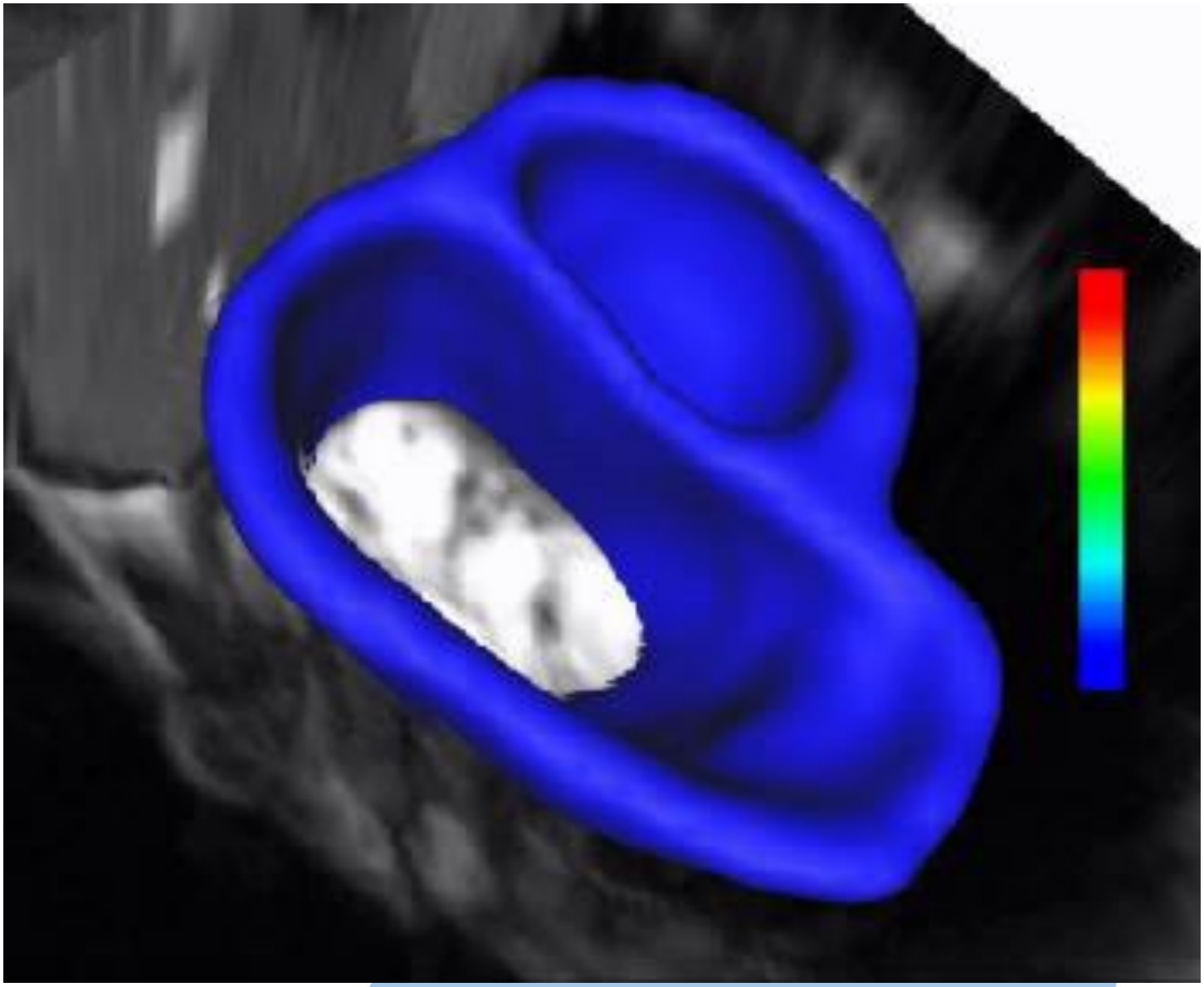






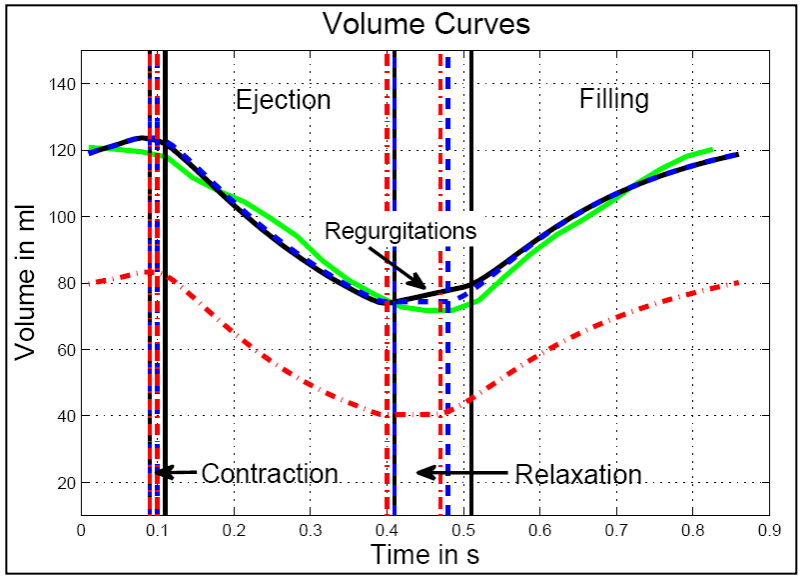
INRA 2008 - Cardo/ESD

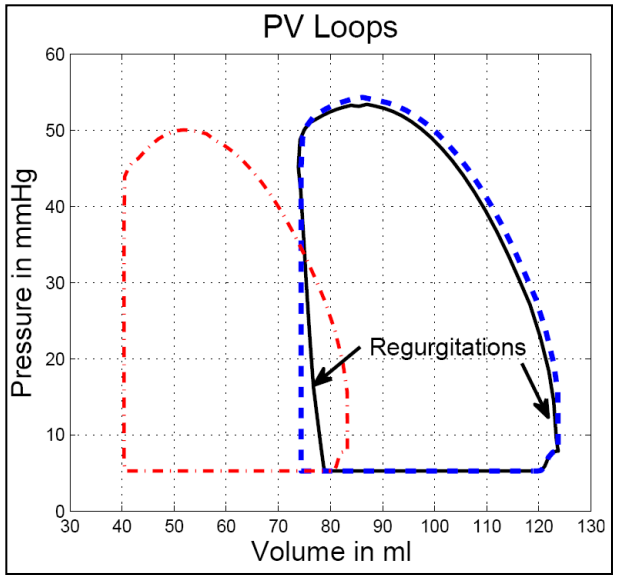
Bambino Gesù
OSPEDALE PEDIATRICO



Bambino Gesù
OSPEDALE PEDIATRICO

Simulating Valve Replacement Therapies: Results



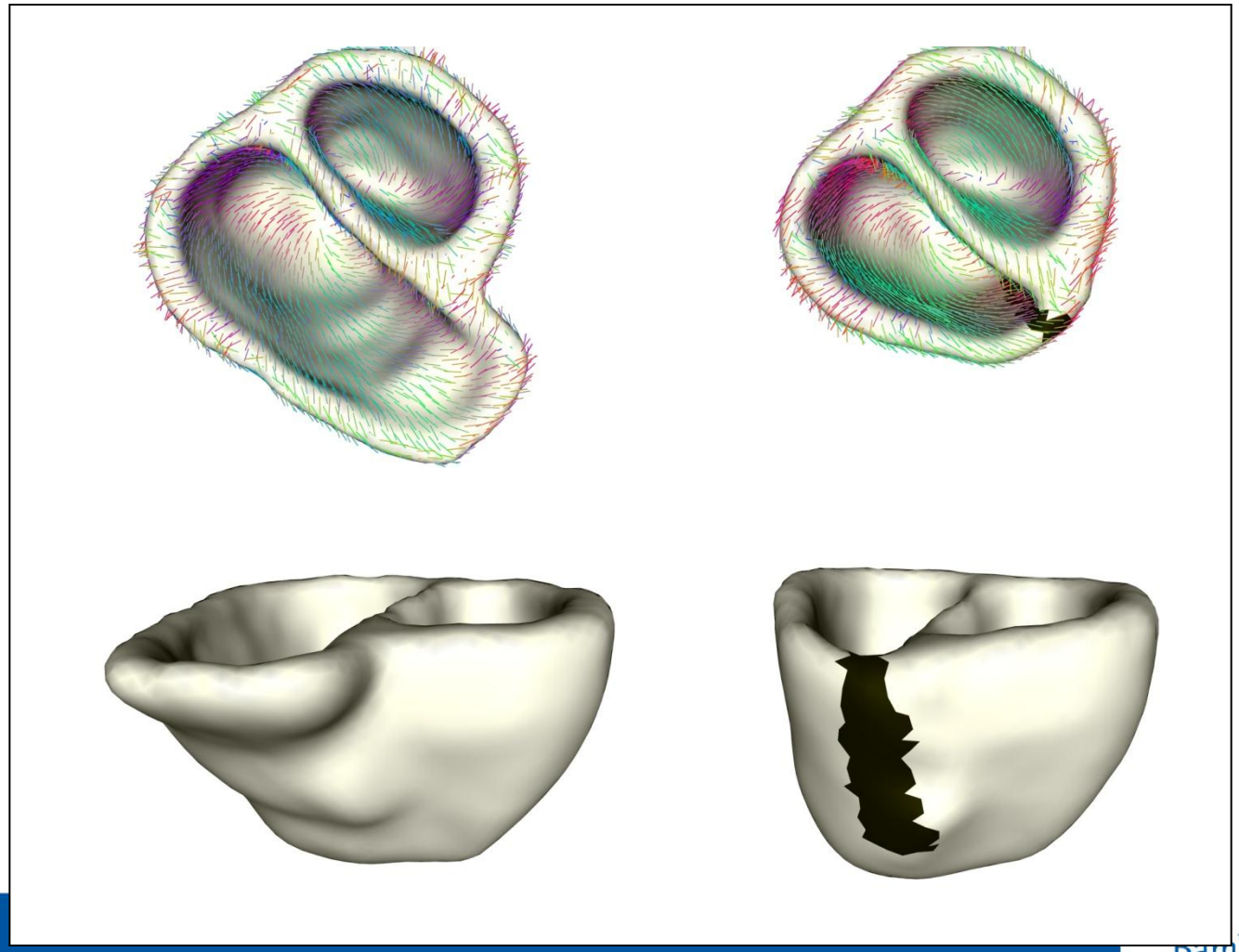


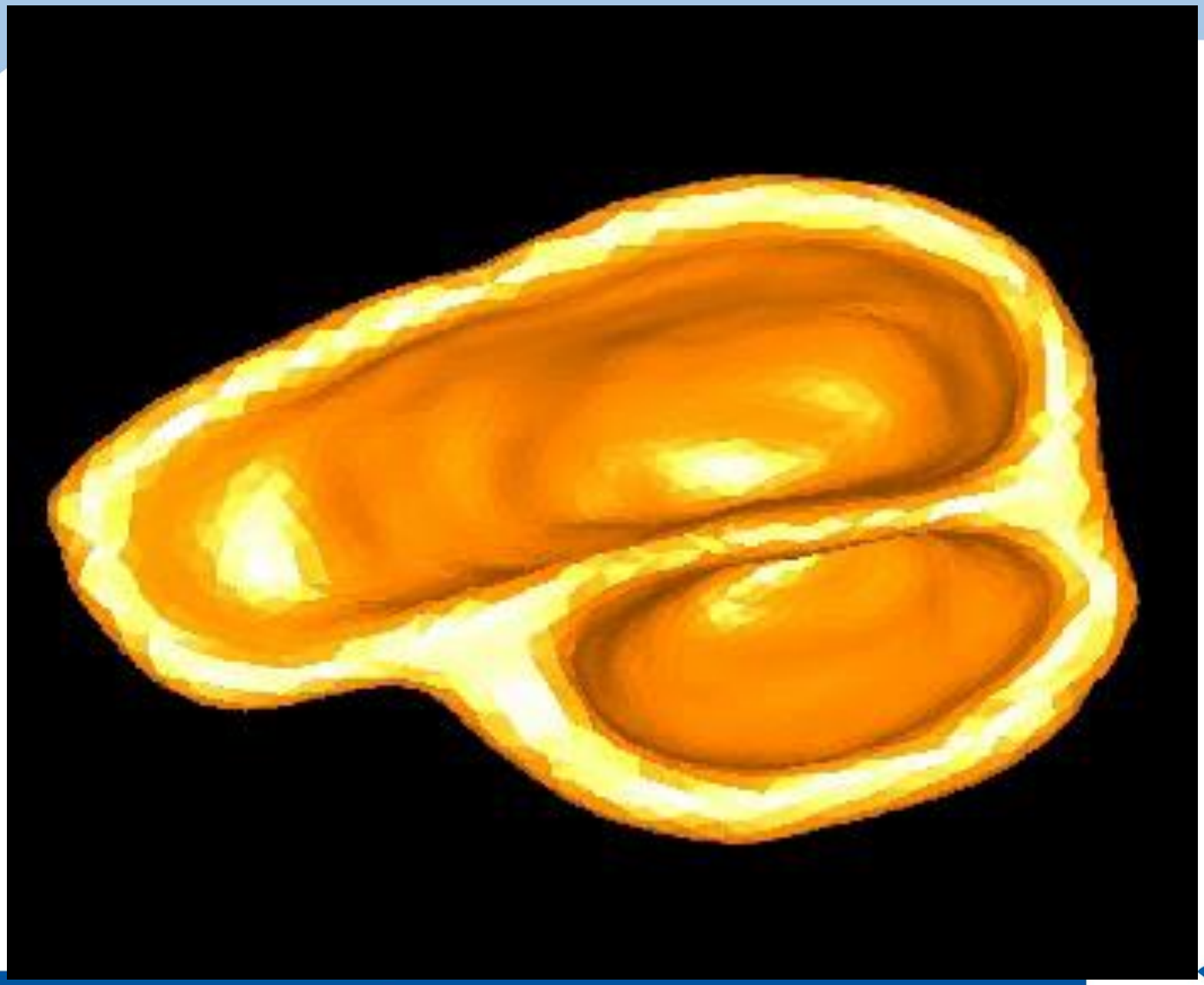
	LVEF	RVEF
Segmentation	61%	41%
Simulation: Preoperative	59%	40%
Simulation: PPVR	59%	40%
Simulation: PVR with RV Reduction	63%	51%

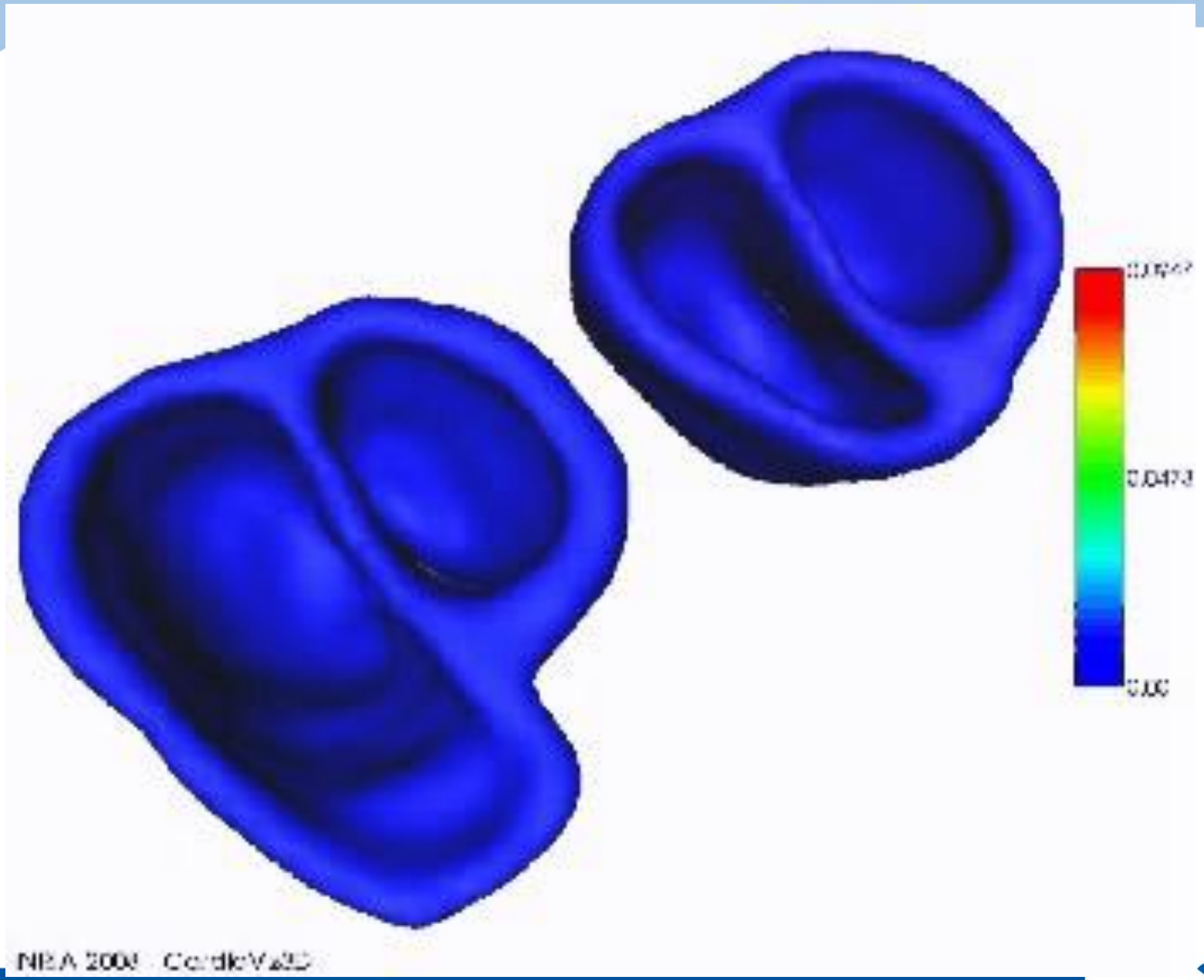
Bambino Gesù
OSPEDALE PEDIATRICO

T. Mansi, B. Andre, M. Lynch, M. Sermesant, H. Delingette, Y. Boudjemline, N. Ayache. VirtualPulmonary Valve Replacement Interventions with a Personalised Cardiac Electromechanical Model, Workshop on 3D Physiological Human, in press

Performing Virtual Volume Reduction Surgery





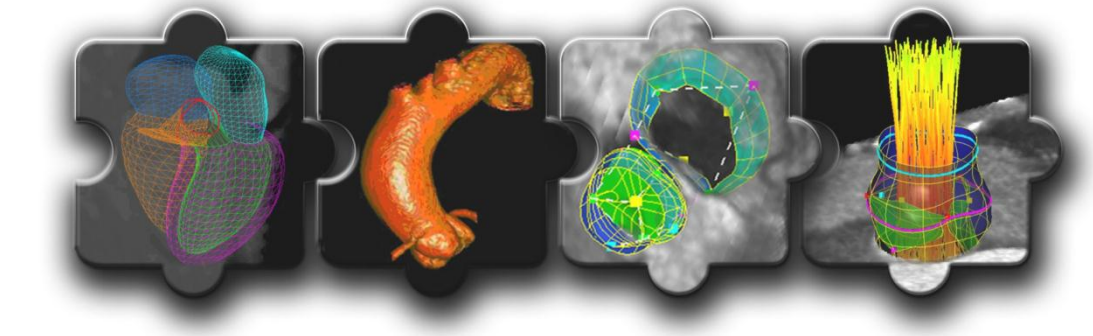


Bambino Gesù
OSPEDALE PEDIATRICO

Sim-e-Child

The Bicuspid Aortic Valve and the Dilatation of the Ascending Aorta

Giacomo Pongiglione, Clinical Coordinator
Bambino Gesù Children's Hospital
Roma



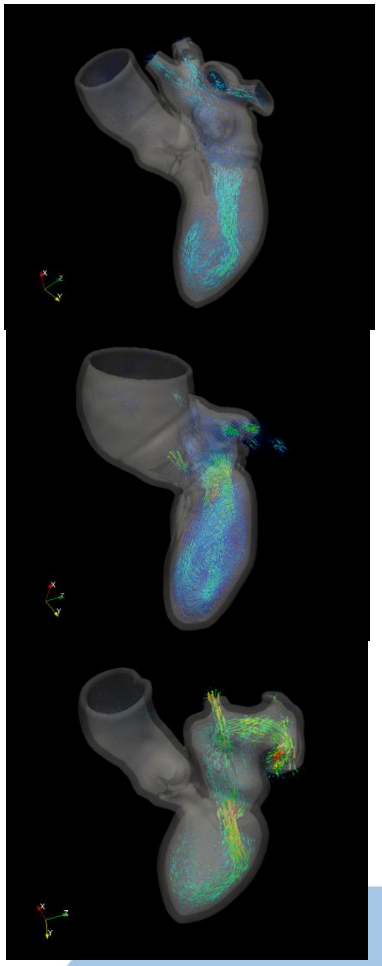
Diastole

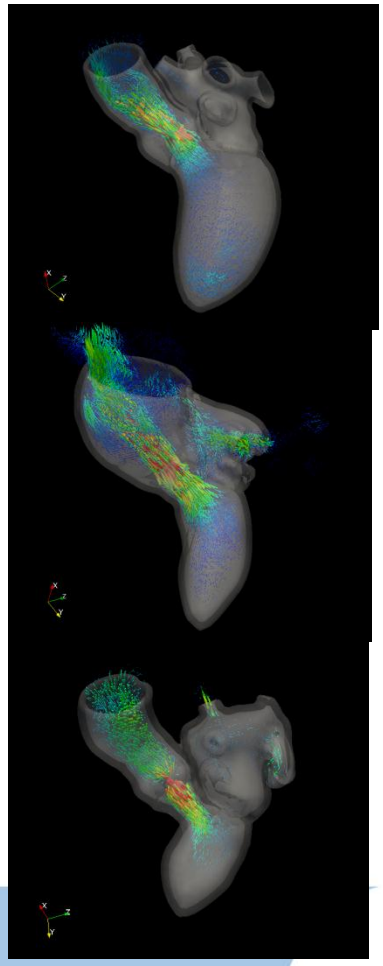
Systole

Normal

Dilated

Bicuspid





Bambino Gesù
OSPEDALE PEDIATRICO

BAV & AORTIC ANEURYSM

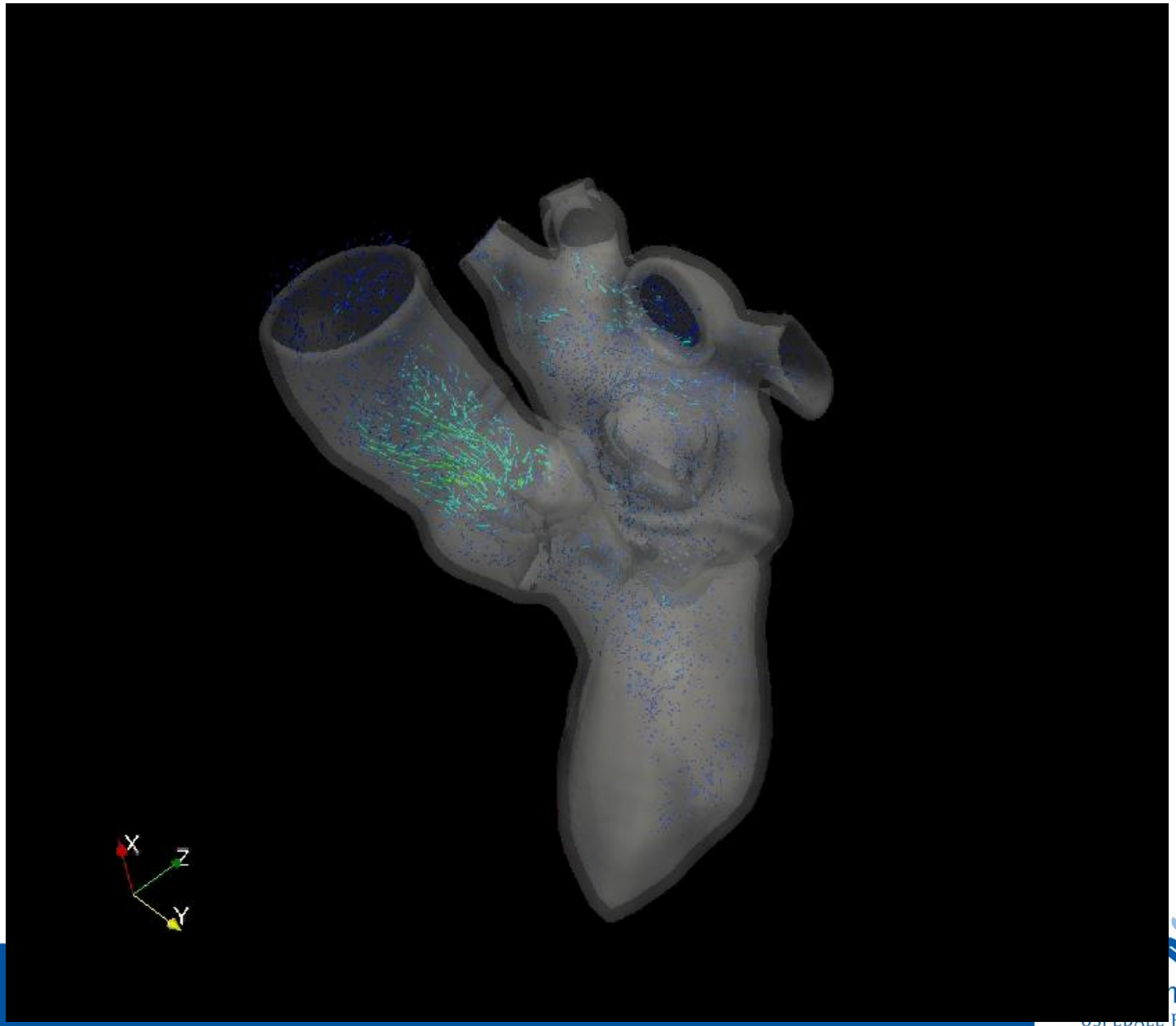
- From an aortic diameter of 40 mm and upwards, maximum size correlates directly with mortality from aortic rupture and dissection
- At diameter 50 – 60 mm, mortality is around 6% / year
- Aim of the medical therapy is to reduce wall stress

BAV & AORTIC ANEURYSM

At present, individual risk assessment:

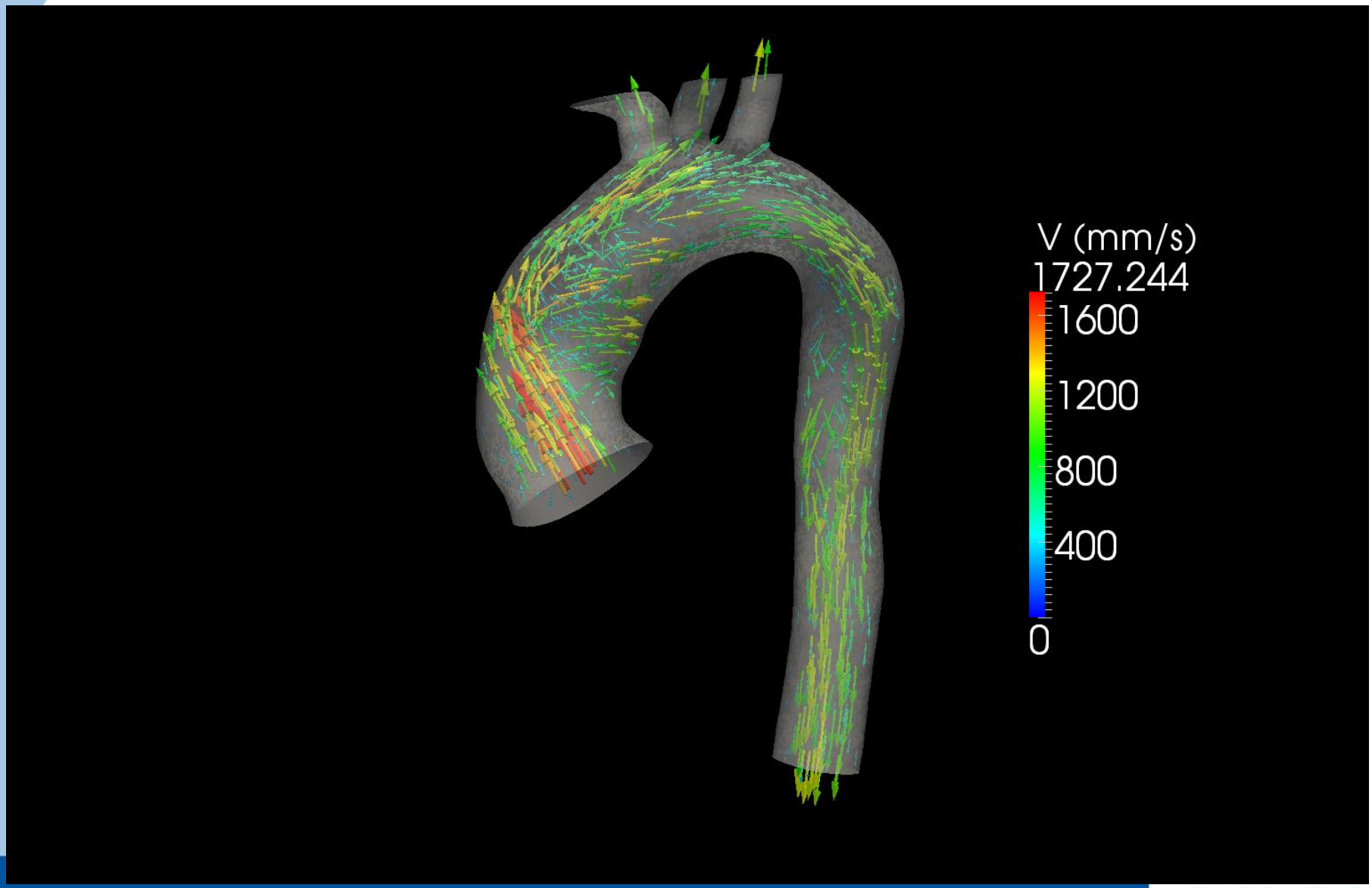
- i Ø > 2.1 cm/m2 (> z +3; n.v. 1.5 cm/m2 ± 0.2)
- Growth rate > 5 mm/y
- Aortic valve morphology
- Corrected or uncorrected Coarctation of the Aorta
- Familiarity
- Genetic Syndromes
- **The current criteria miss 30 – 40 % of dissections**

VELOCITY VECTORS

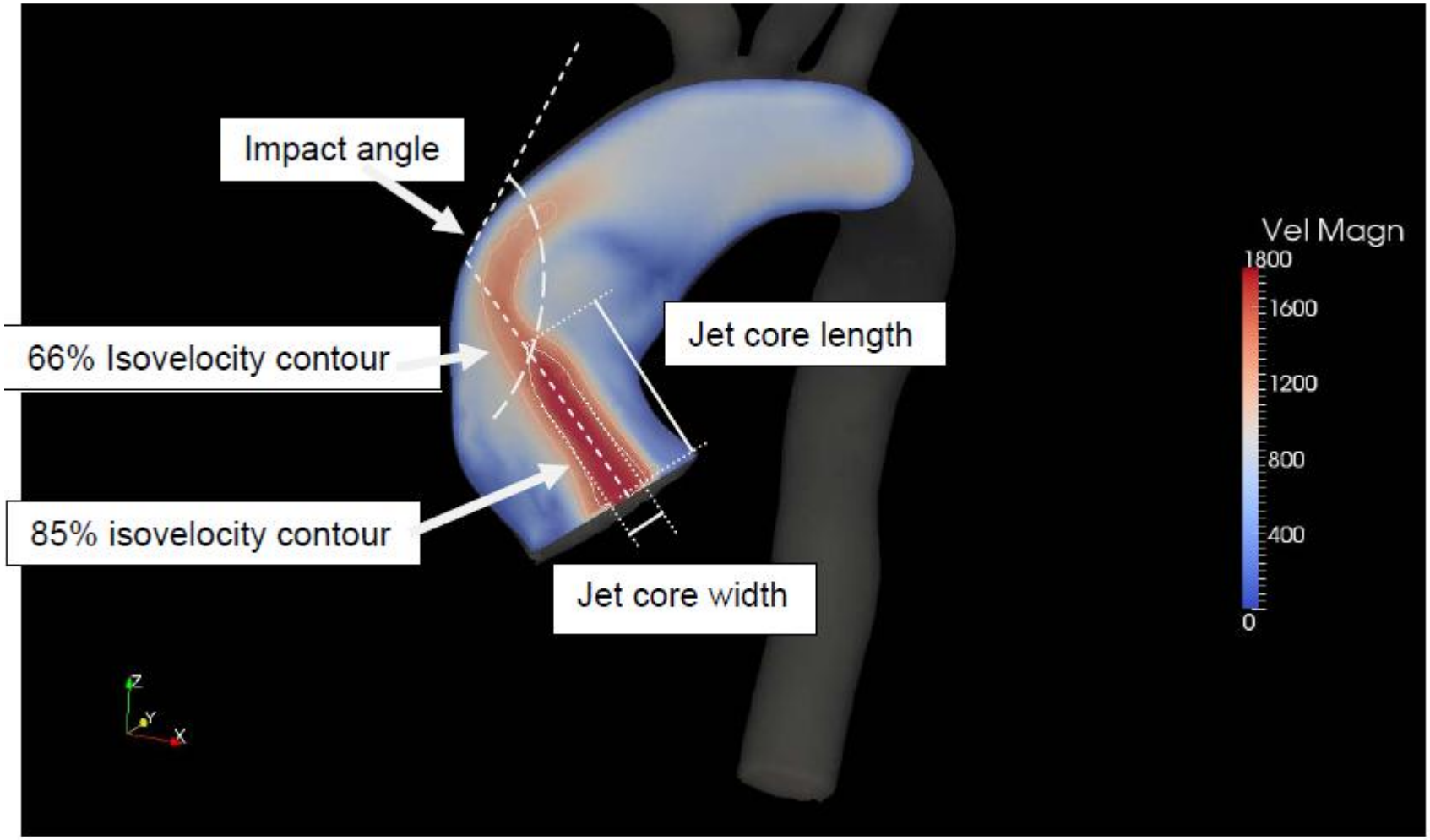


VORTICITY

BAV 1004

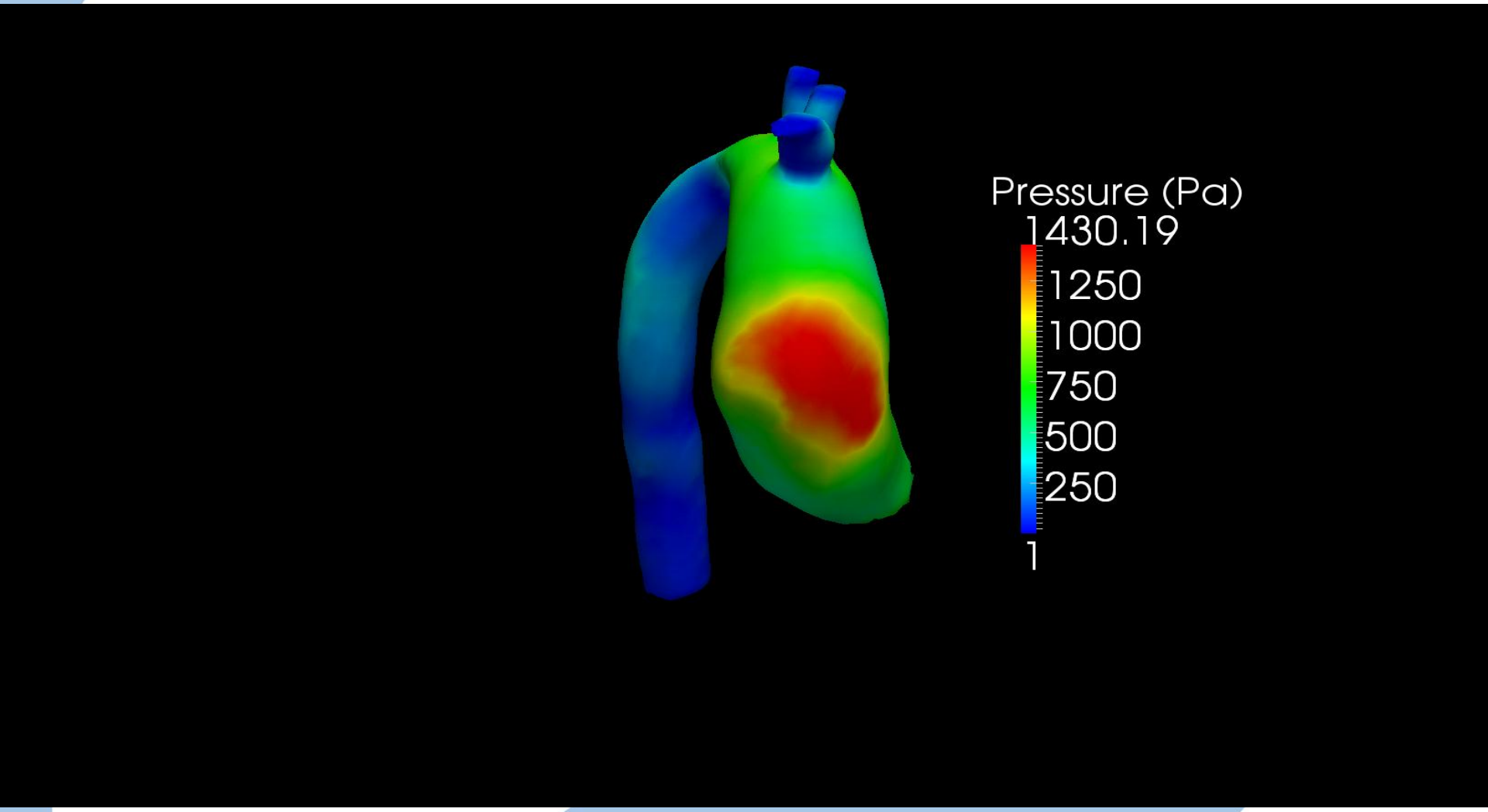


Jet-specific Parameters Measured in the AAo



Bambino Gesù
OSPEDALE PEDIATRICO

BAV 1004

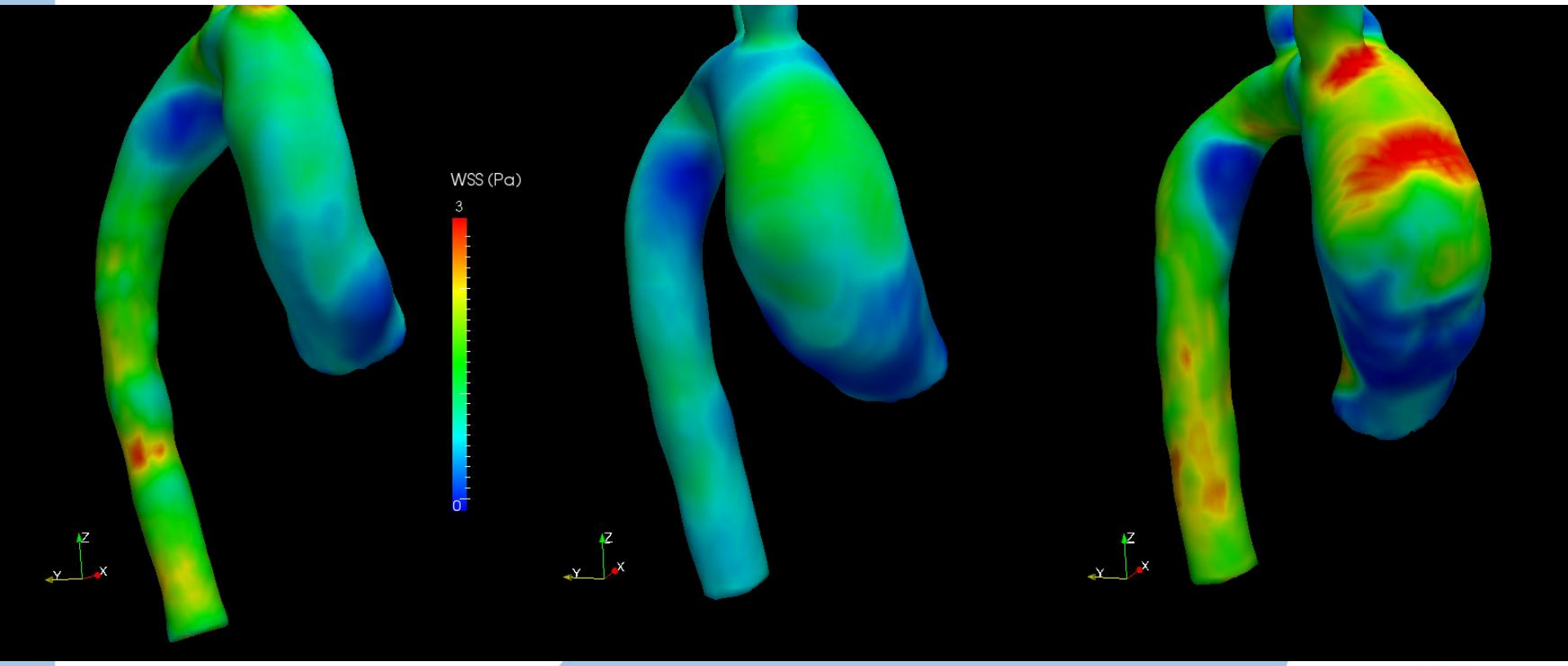


- **Pa = 1N/m2 N= Kg/ m s2 1 Kpa = 7.5 mmHg**

Bambino Gesù
OSPEDALE PEDIATRICO

Wall Shear Stress (Mid Systole)

Normal 1019 BAV1004 BAV1008



The modulus of elasticity is a datum that describes how a material will deform or break subjected to a force or stress.

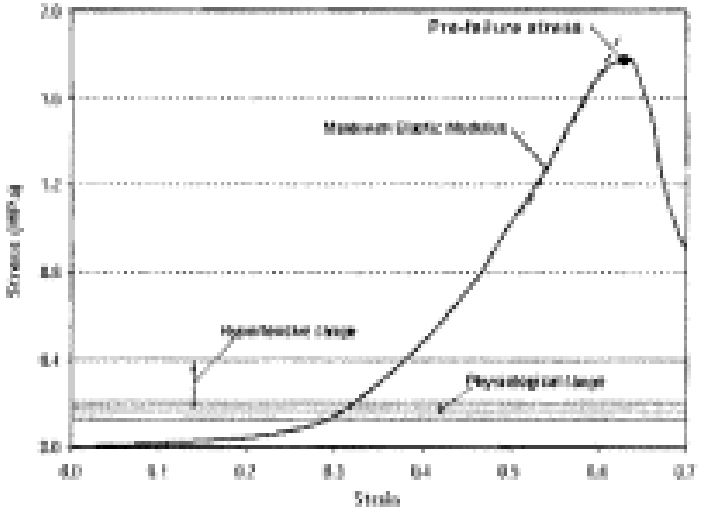


FIGURE 1. Principles of calculating the physiologic range, hypertensive range, and MEM.

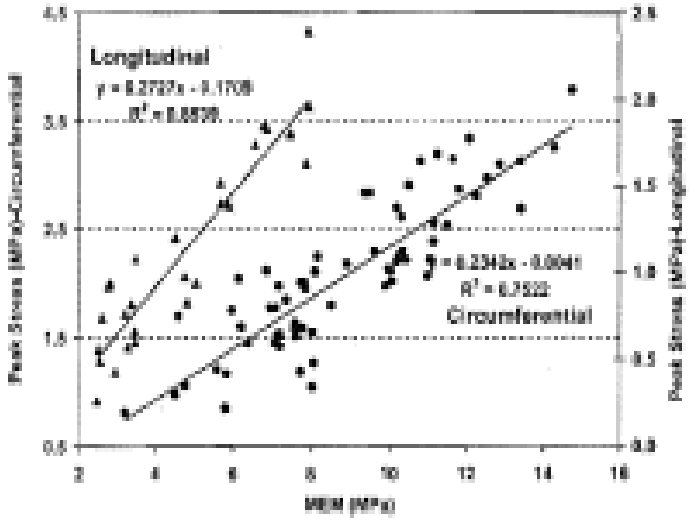


FIGURE 3. Correlation between MEM and peak stress in the circumferential and longitudinal orientations. *MEM*, Maximum elastic modulus.

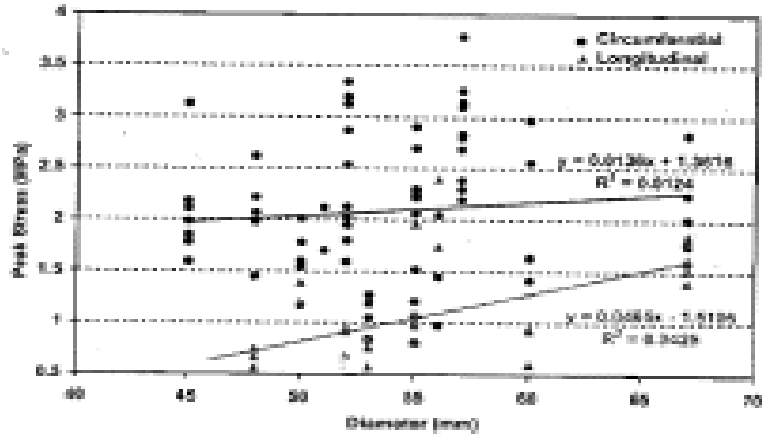


FIGURE 4. Effect of the aneurysm diameter on peak stress in the circumferential and longitudinal orientations.

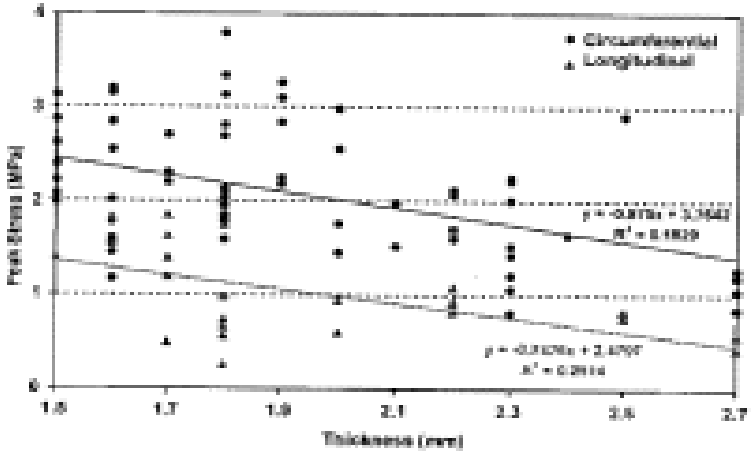
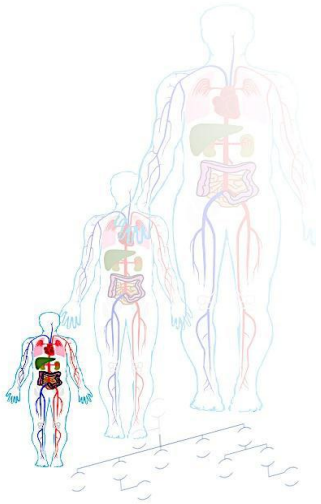


FIGURE 5. Effect of the aneurysm wall thickness on peak stress in the circumferential and longitudinal orientations.

Bambino Gesù
OSPEDALE PEDIATRICO

Call FP7-ICT-2011-9 – Objective 5.2 – Proposal No. 600932



MD-Paedigree

Model-Driven European Paediatric Digital Repository

Bruno Dallapiccola/OPBG (Coordinator)
Giacomo Pongiglione/OPBG (Clinical Coordinator)
Edwin Morley-Fletcher/Lynkeus (Project Manager)
Michael Suehling/Siemens (Modelling and Simulation)
David Manset/Maat (MD-Paedigree Infostructure)

Bambino Gesù
OSPEDALE PEDIATRICO

Evaluation Hearing: Covent Garden, Place Rogier 16, Brussels
20th June 2012

CONCLUSIONS 1

Ontology-based Cloud technologies provide a new multidimensional information environment and powerful tools for collaborative data handling and analysis

CONCLUSIONS 2

The digital patient (VPH) is the virtual representation of the integration of the computer models of the different organs, apparatus and diseases

New technological level in Biomedical research

THANK YOU FOR YOUR ATTENTION

Bambino Gesù
OSPEDALE PEDIATRICO