e-Seminar series

CompBioMed

A Centre of Excellence in Computational Biomedicine

# e-Seminar #23

## Supercomputer-based in-silico clinical trials in cardiac therapies towards exascale computing

**27 May 2022**

The e-Seminar will start at 2pm CEST / 1pm BST


Presenter:
**Mariano Vázquez**
**(Barcelona Supercomputing Center, ELEM Biotech)**

Moderator:
**Tim Weaving**
**(University College London)**



[T]his project has received funding from the European Union's [H]orizon 2020 research and innovation programme under grant agreement No 823712


INSILICO WORLD

https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with:

VPH Institute
Building the Virtual Physiological Human

CompBioMed

A Centre of Excellence in Computational Biomedicine

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# SUPERCOMPUTER-BASED IN-SILICO CLINICAL TRIALS

# THE FUTURE OF MEDICINE

MARIANO VÁZQUEZ
CSO/CTO - ELEM BIOTECH
TEAM LEADER - BARCELONA SUPERCOMPUTING CENTER

ELEM

THE VIRTUAL HUMANS
FACTORY

POWERED BY BSC Barcelona Supercomputing Center Centro Nacional de Supercomputación

# SUPERCOMPUTER-BASED IN-SILICO CLINICAL TRIALS

# THE FUTURE OF MEDICINE NOW

MARIANO VÁZQUEZ
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THE VIRTUAL HUMANS FACTORY

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Centro Nacional de Supercomputación

# MARENOSTRUM IV

166.000 CORES
11.5 PFLOPS
1.3 MW / YEAR

HOSTED BY THE BARCELONA SUPERCOMPUTING CENTER

**HARDWARE** SETUP AND MAINTENANCE
**SOFTWARE** DEVELOPMENT AND EFFICIENCY
**DATA** MANAGEMENT

*MARENOSTRUM IV SUPERCOMPUTER*

# BARCELONA SUPERCOMPUTING CENTER

600+ RESEARCHERS
SPANISH PUBLIC CENTER

TIER-0 EUROPEAN SUPERCOMPUTING NETWORK (PRACE)

APPLIED COMPUTATIONAL SCIENCE SINCE 2005

*BSC CORPORATE BULDING*

# ALYA DEV TEAM

50 RESEARCHERS
MATHEMATICIANS, PHYSICISTS, ENGINEERS, PROGRAMMERS...

SENIOR AND PHD STUDENTS

BORN WITH BSC IN 2005


*FLAMANG, B., MARRAS, S., ET AL. 2020. REMORAS PICK WHERE THEY STICK ON BLUE WHALES. JOURNAL OF EXPERIMENTAL BIOLOGY, 223, JEB226654. DOI:10.1242/JEB.226654*

# ELEM BIOTECH

BSC'S SPINOFF COMPANY

BIOMEDICAL SOFTWARE TECHNOLOGY

INSILICO CLINICAL TRIALS

HPC-CLOUD BASED SIMULATIONS

CELL, TISSUE AND ORGAN LEVEL


*ELEM'S VIRTUAL HUMANS*

# THE TECHNICAL CHALLENGE

RE-CREATE **BIOLOGICAL SYSTEMS** IN A COMPUTER

THE MORE **COMPLEX** THE SYSTEM, THE **LARGER** THE COMPUTER

THE **LARGER** THE COMPUTER, THE MORE **EFFICIENT** THE CODE

# A VIRTUAL HUMANS PLATFORM

SUPERCOMPUTING EFFICIENCY
+
ACCURATE MULTISCALE / MULTIPHYSICS MODELLING
+
VIRTUAL POPULATION GENERATION

---

SUPERCOMPUTER BASED **IN-SILICO CLINICAL TRIALS**
TO OPTIMIZE AND PERSONALIZE MEDICAL THERAPIES

# A VIRTUAL HUMANS PLATFORM

THE USER FOLLOWS THESE STEPS

SELECT THE POPULATION
SELECT THE PRIMARY DISEASE
SELECT THE COMMORBIDITIES

LAUNCH THE SUPERCOMPUTER-BASED IN-SILICO CLINICAL TRIAL ON THE SELECTED VIRTUAL COHORT

WAIT FROM DAYS TO WEEKS (DEPENDING ON THE TESTS)

ANALYSE THE RESULTS AS THEY COME
REPEAT

# BACKGROUND

# ALYA
## PARALLEL MULTISCALE SIMULATION CODE


USED IN INDUSTRY RELATED PROJECTS: AEROSPACE, ENERGY, ENVIRONMENT AND... **BIOMEDICAL**

THE ONLY MULTIPHYSICS MULTISCALE CODE FOR BIOMEDICAL USE AT ORGAN LEVEL BORN AND DEVELOPED IN A SUPERCOMPUTING CENTER

*VÁZQUEZ, M., HOUZEAUX, G., KORIC, S., ARTIGUES, A., AGUADO-SIERRA, J., ARÍS, R., MIRA, D., CALMET, H., CUCCHIETTI, F., OWEN, H. AND TAHA, A., 2016. ALYA: MULTIPHYSICS ENGINEERING SIMULATION TOWARD EXASCALE. JOURNAL OF COMPUTATIONAL SCIENCE, 14, PP.15-27.*

# ALYA RED

SIMULATION TOOLS FOR
BIOMEDICAL RESEARCH

INSILICO CLINICAL TRIALS
AND DIAGNOSE

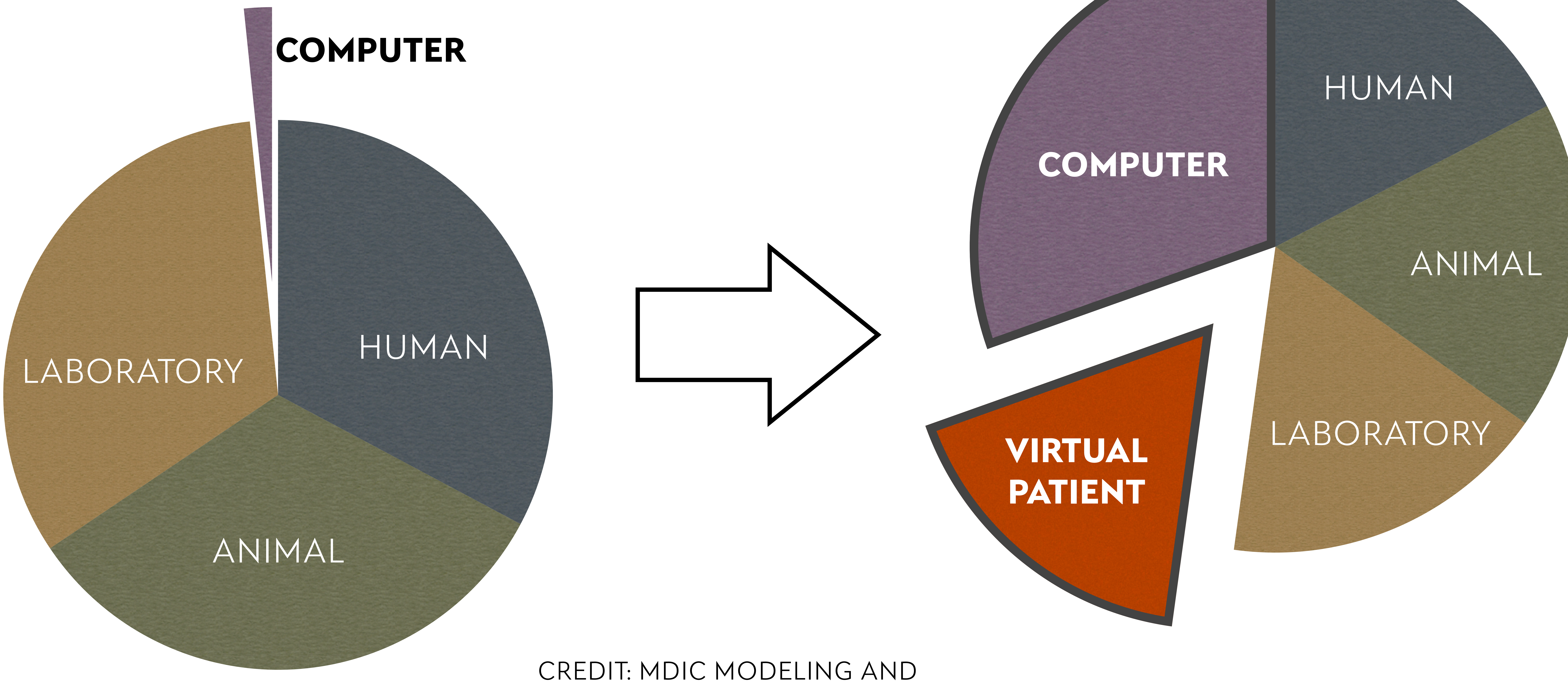
ORGAN / TISSUE LEVEL

COMPLEX PROBLEMS WHICH REQUIRE SUPERCOMPUTERS

CARDIOVASCULAR, RESPIRATORY, ...
FOR PHARMA, MEDTECH, ...

# THE VIRTUAL HUMAN

## FDA VISION




CREDIT: MDIC MODELING AND SIMULATION PROJECT

ELEM

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

# THE VIRTUAL HUMAN

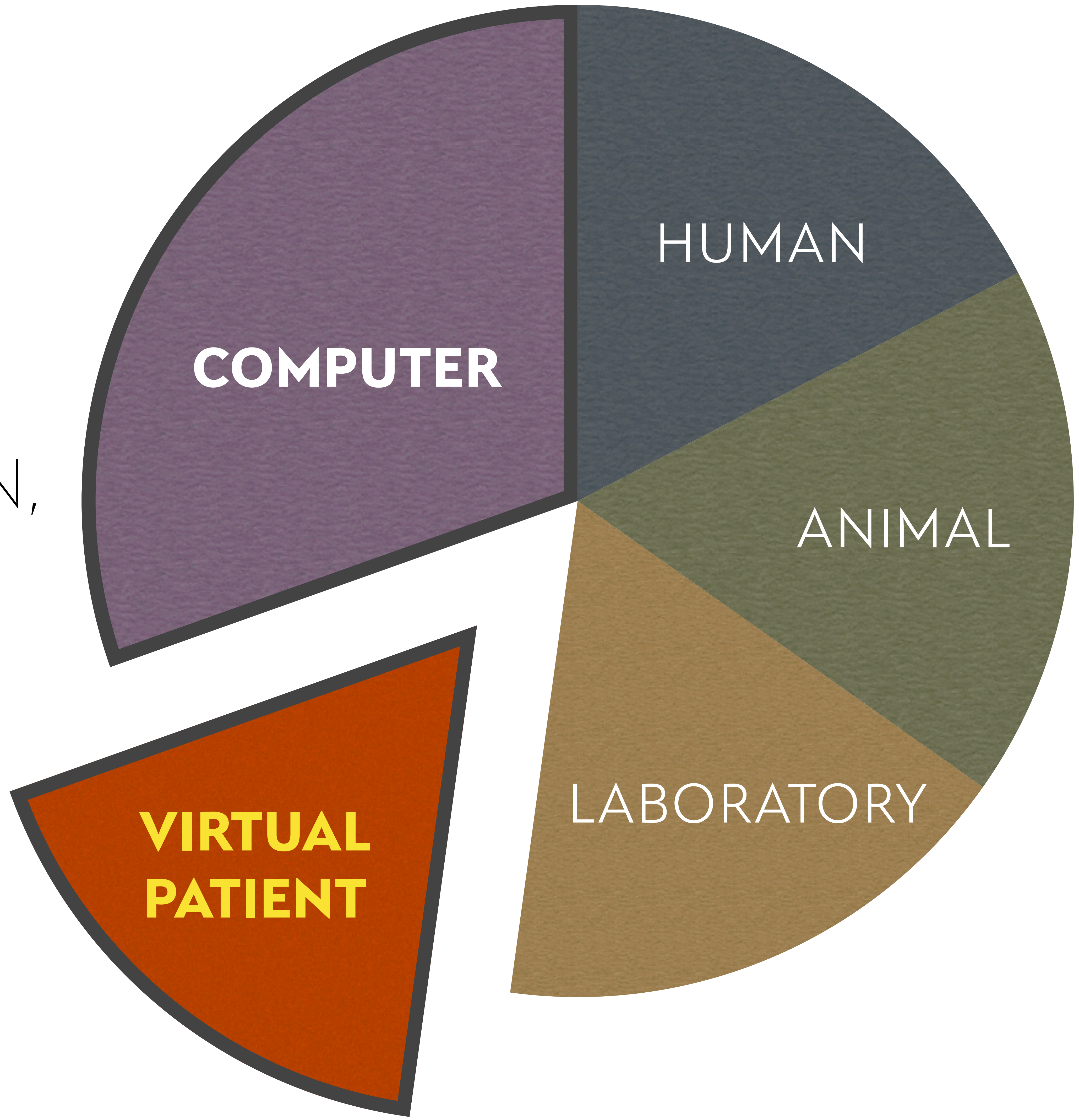
## FDA VISION

COMPLEXITY BOOST:

MODEL NOT JUST THE ISOLATED THERAPY BUT DO IT **ON THE PATIENT**: SYSTEM, ORGAN, TISSUE, CELL

IMPLIES **COMPREHENSIVE** MODELLING: COMORBIDITIES, PATIENT VARIABILITY, ETC.

REQUIRES SPECIFIC **IN-VIVO AND EXPERIMENTAL** VALIDATION ON CONTEXTS OF USE



# EXAMPLES

*WATCH OUR VIDEO CLIP ABOUT "THE VIRTUAL HUMAN": HTTPS://YOUTU.BE/GS9PLDZ8OKW*

# THE CARDIOVASCULAR SYSTEM

COLLABORATORS:

THE VISIBLE HEART LAB - UNIV. OF MINNESOTA(US)
CENTRO NACIONAL DE INVESTIGACION CARDIOVASCULAR (SPAIN)
HOSPITAL DE SANT PAU (SPAIN)
UNIVERSITY OF OXFORD (UK)
UNIVERSITAT POMPEU FABRA (SPAIN)
UNIVERSITAT POLITECNICA DE VALENCIA (SPAIN)
GEORGE MASON UNIVERSITY (US)
UNIVERSITY COLLEGE LONDON (UK)
SAN DIEGO STATE UNIVERSITY (US)
FDA (US)

# THE VIRTUAL HEART

## ENGINEERING VIEWPOINT

ELECTRO
PHYSIOLOGY

model is solved implicitly with either a Backward Euler or a Crank-Nicolson scheme. From numerical experiments we observed that the main limitation solving the electrophysiological model was the time limitation of the tissue model. The proposed combined scheme permits to simulate cardiac electrical propagation both efficient and accurate enough.

**Computational implementation of electrophysiology model**

$$\textbf{Cell model}(\Delta\phi^*): \quad \frac{\Delta\phi^*}{\Delta t} + \mathbf{I}_{ion}(\phi) = 0$$

$$\textbf{Tissue model}(\Delta\tilde{\phi}): \quad \left(\frac{\mathbf{M}}{\Delta t} + \mathbf{K}\right)\Delta\tilde{\phi} = -\mathbf{K}\phi^*, \text{ where } \Delta\phi^* = \phi^* - \phi^n$$

$$\textbf{Update}(\phi^{n+1}): \quad \phi^{n+1} = \phi^n + \Delta\phi^* + \Delta\tilde{\phi}.$$

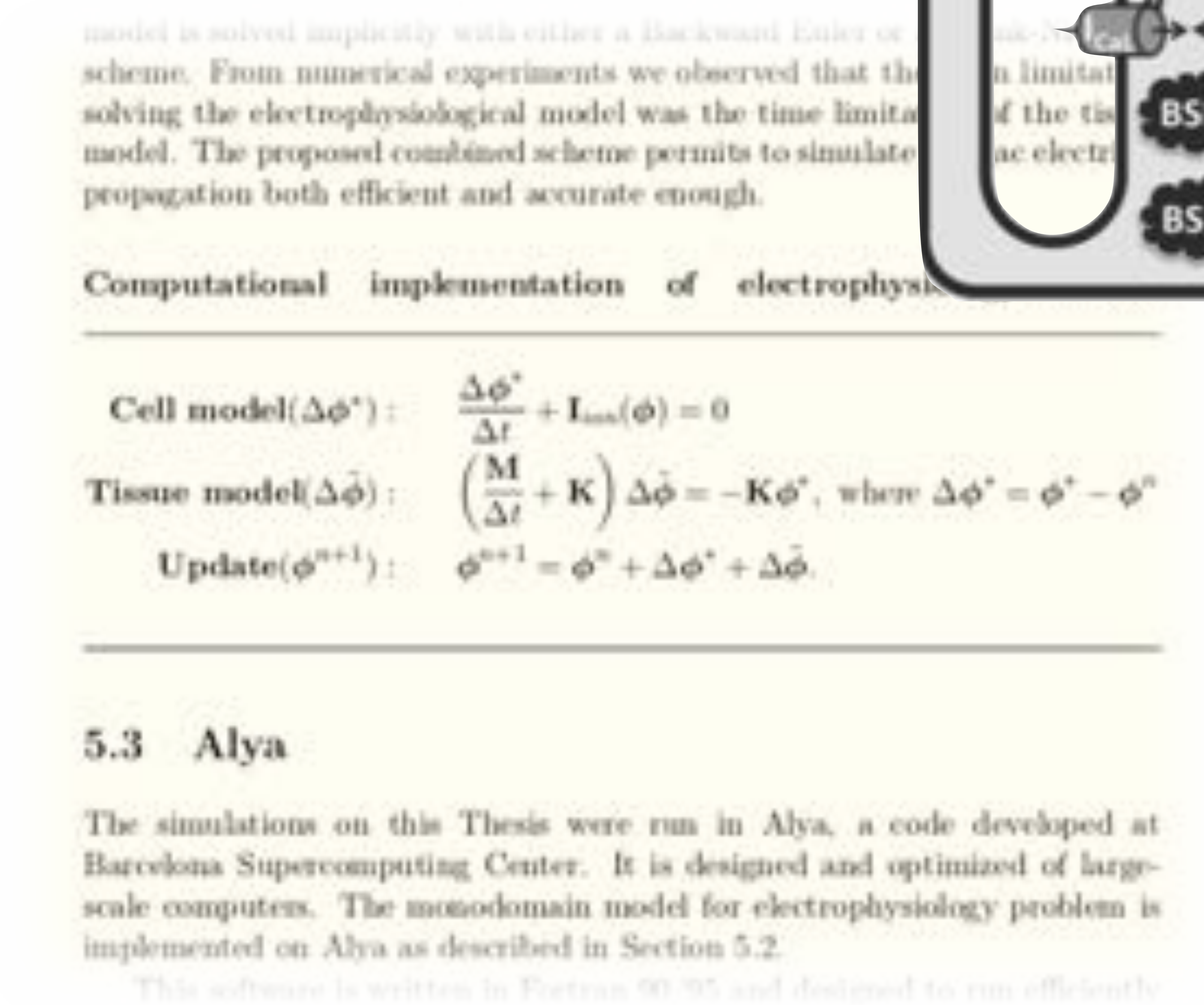
### 5.3 Alya

The simulations on this Thesis were run in Alya, a code developed at Barcelona Supercomputing Center. It is designed and optimized of large-scale computers. The monodomain model for electrophysiology problem is implemented on Alya as described in Section 5.2.

This software is written in Fortran 90/95 and designed to run efficiently

# THE VIRTUAL HEART
## ENGINEERING VIEWPOINT

ELECTRO PHYSIOLOGY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**Computational implementation of electrophysi...**

**Cell model**$(\Delta\phi^*)$ : $\frac{\Delta\phi^*}{\Delta t} + \mathbf{I}_{ion}(\phi) = 0$

**Tissue model**$(\Delta\tilde{\phi})$ : $\left(\frac{\mathbf{M}}{\Delta t} + \mathbf{K}\right)\Delta\tilde{\phi} = -\mathbf{K}\phi^*$, where $\Delta\phi^* = \phi^* - \phi^n$

**Update**$(\phi^{n+1})$ : $\phi^{n+1} = \phi^n + \Delta\phi^* + \Delta\tilde{\phi}$.

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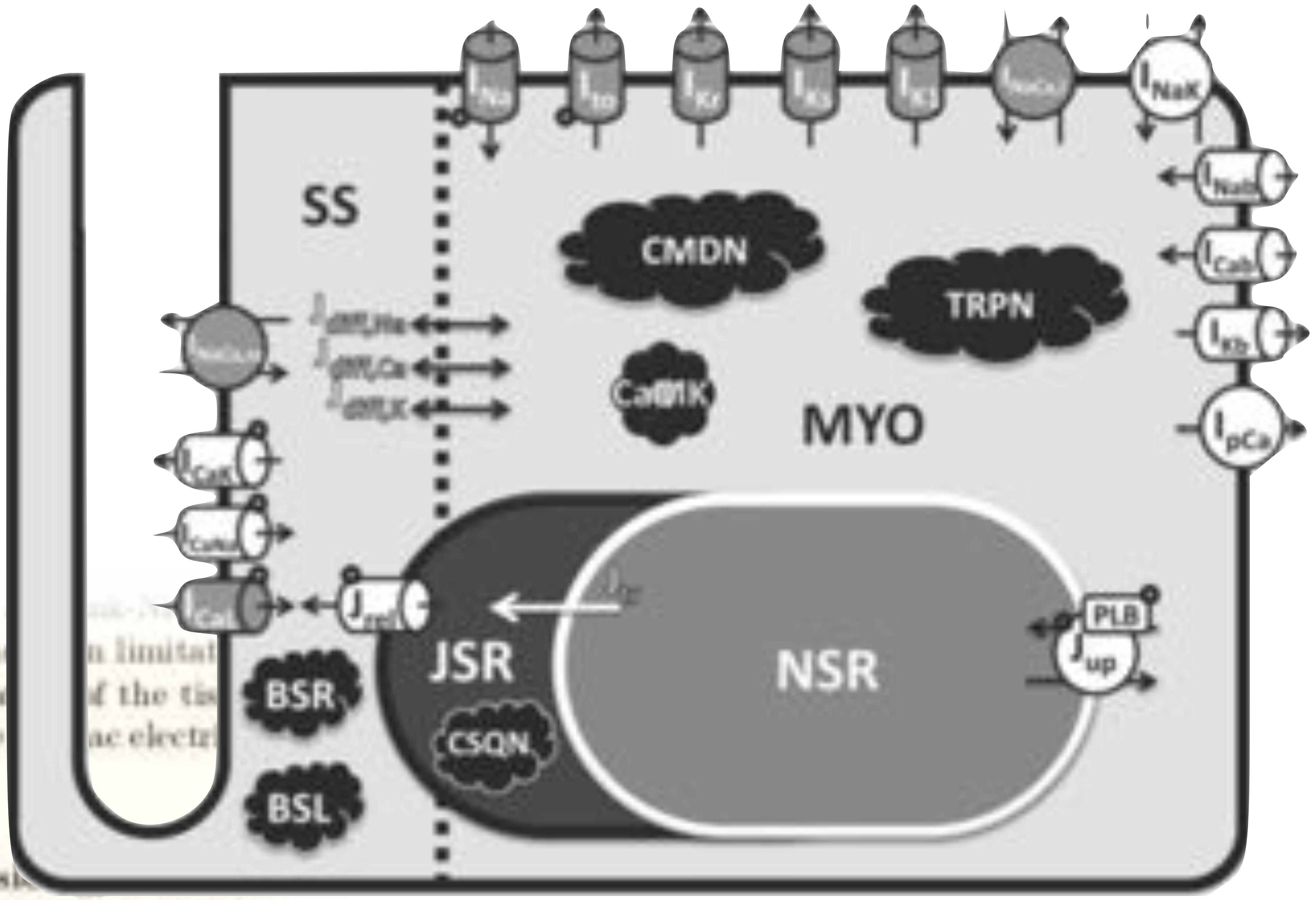



O’HARA-RUDY CELLULAR DYNAMICS MODEL

50 ODES SOLVED AT EACH GAUSS POINT

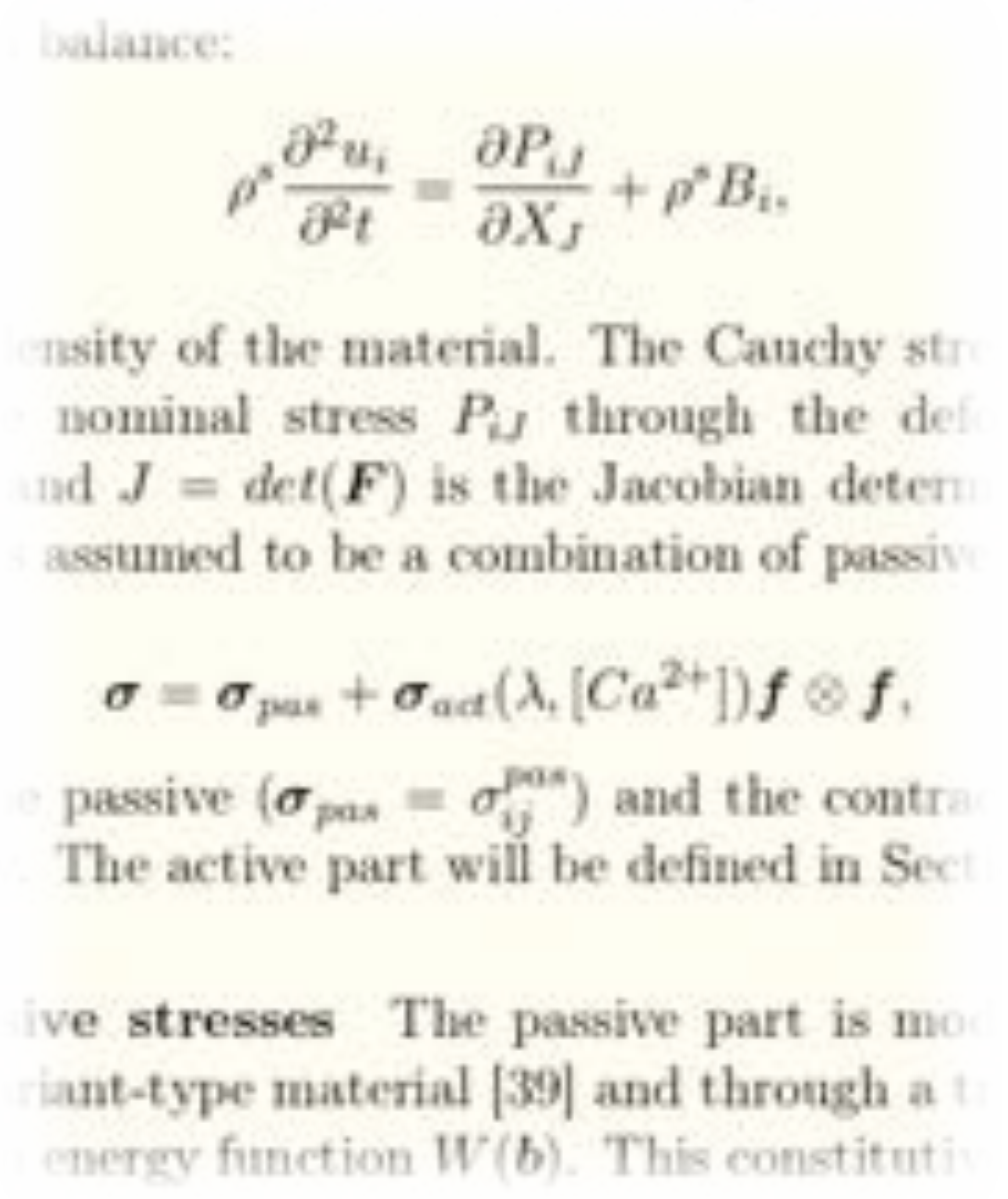
# THE VIRTUAL HEART

## ENGINEERING VIEWPOINT

ELECTRO PHYSIOLOGY

MECHANICS

ELECTRO-MECHANICAL COUPLING


balance:

$$\rho^s \frac{\partial^2 u_i}{\partial^2 t} = \frac{\partial P_{iJ}}{\partial X_J} + \rho^s B_i,$$

nsity of the material. The Cauchy st
nominal stress $P_{iJ}$ through the de
nd $J = det(\boldsymbol{F})$ is the Jacobian deter
assumed to be a combination of passi

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{pas} + \boldsymbol{\sigma}_{act}(\lambda, [Ca^{2+}])\boldsymbol{f} \otimes \boldsymbol{f},$$

passive ($\boldsymbol{\sigma}_{pas} = \sigma_{ij}^{pas}$) and the contr
The active part will be defined in Sec

**ive stresses** The passive part is mo
iant-type material [39] and through a
energy function $W(\boldsymbol{b})$. This constituti

SANTIAGO, A., AGUADO-SIERRA, J., ZAVALA-AKÉ, M., DOSTE-BELTRAN, R., GÓMEZ, S., ARÍS, R., CAJAS, J.C., CASONI, E. AND VÁZQUEZ, M., 2018. FULLY COUPLED FLUID-ELECTRO-MECHANICAL MODEL OF THE HUMAN HEART FOR SUPERCOMPUTERS. INTERNATIONAL JOURNAL FOR NUMERICAL METHODS IN BIOMEDICAL ENGINEERING, 34(12), P.E3140.

# THE VIRTUAL HEART
## ENGINEERING VIEWPOINT

ELECTRO PHYSIOLOGY

MECHANICS

BLOOD

FLUID-SOLID INTERACTION

ELECTRO-MECHANICAL COUPLING

*SANTIAGO, A., AGUADO-SIERRA, J., ZAVALA-AKÉ, M., DOSTE-BELTRAN, R., GÓMEZ, S., ARÍS, R., CAJAS, J.C., CASONI, E. AND VÁZQUEZ, M., 2018. FULLY COUPLED FLUID-ELECTRO-MECHANICAL MODEL OF THE HUMAN HEART FOR SUPERCOMPUTERS. INTERNATIONAL JOURNAL FOR NUMERICAL METHODS IN BIOMEDICAL ENGINEERING, 34(12), P.E3140.*

# THE VIRTUAL HEART

## ENGINEERING VIEWPOINT

ANATOMY & PHYSIOLOGY

ELECTRO PHYSIOLOGY

MECHANICS

BLOOD

FLUID-SOLID INTERACTION

ELECTRO-MECHANICAL COUPLING

# THE VIRTUAL HEART

## ENGINEERING VIEWPOINT

ANATOMY & PHYSIOLOGY

ELECTRO PHYSIOLOGY

MECHANICS

BLOOD

RESULTS ANALYSIS

VALIDATION & VERIFICATION

# THE VIRTUAL HEART
## ENGINEERING VIEWPOINT

CONTEXT OF USE

OR

WHAT ARE YOU DOING?

ANATOMY & PHYSIOLOGY

MULTI-PHYSICS MODELLING

RESULTS ANALYSIS

VALIDATION & VERIFICATION

QUANTITY OF INTEREST I.E. BIOMARKER

OR

WHAT DO YOU WANT?

# THE VIRTUAL HEART

## VALIDATION & VERIFICATION

| | | | |
|---|---|---|---|
| SCIENTIFIC VERIFICATION | ACADEMIC CODE SELF VERIFICATION<br>ANALYTIC OR MANUFACTURED SOLUTIONS<br>CONVERGENCE ANALYSIS | CONTINUUM | GENERAL |
| SCIENTIFIC VALIDATION | FROM LITERATURE<br>FREQUENTLY SIMPLE CASES<br>MOSTLY SINGLE PHYSICS | CONTINUUM | GENERAL |
| EXPERIMENTAL VALIDATION | AD HOC BENCHTOP (IN VITRO / EX VIVO) EXPERIMENTS<br>ASME VV40 VALIDATION PROTOCOL<br>HIGH CONTROL AND MAYBE MULTI PHYSICS<br>BEST OUTCOME: MDDT FDA CERTIFICATION | CAMPAIGN | CONTEXT OF USE |
| CLINICAL VALIDATION | AD HOC CLINICAL (IN VIVO) MEASUREMENTS<br>CLINICAL VALIDATION PROTOCOL<br>LOW CONTROL AND MAYBE MULTI PHYSICS<br>BEST OUTCOME: CLINICAL VALIDATION PAPER | CAMPAIGN | CONTEXT OF USE |

# THE VIRTUAL HEART
## ANATOMY & PHYSIOLOGY


PATIENTS DATABASE

FEMALE, MALE, CHILDREN

WITH THE VHL, UNIV. OF MINNESOTA

# THE VIRTUAL HEART
## ANATOMY & PHYSIOLOGY

**VIRTUAL**
PATIENTS DATABASE

FEMALE, MALE, CHILDREN

HEALTH, DISEASE &
TREATMENT

# ANATOMY AND PHYSIOLOGY

## SETTING UP THE SCENARIO

SEMI-EMPIRICAL RULE BASED MODEL
FIBRES ARE ORIENTED ALONG HELICES OF OPPOSITE SENSE IN EPICARDIUM AND ENDOCARDIUM