Modelica language – a promising tool for publishing and sharing of biomedical models

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creative connections
charles multimedia education

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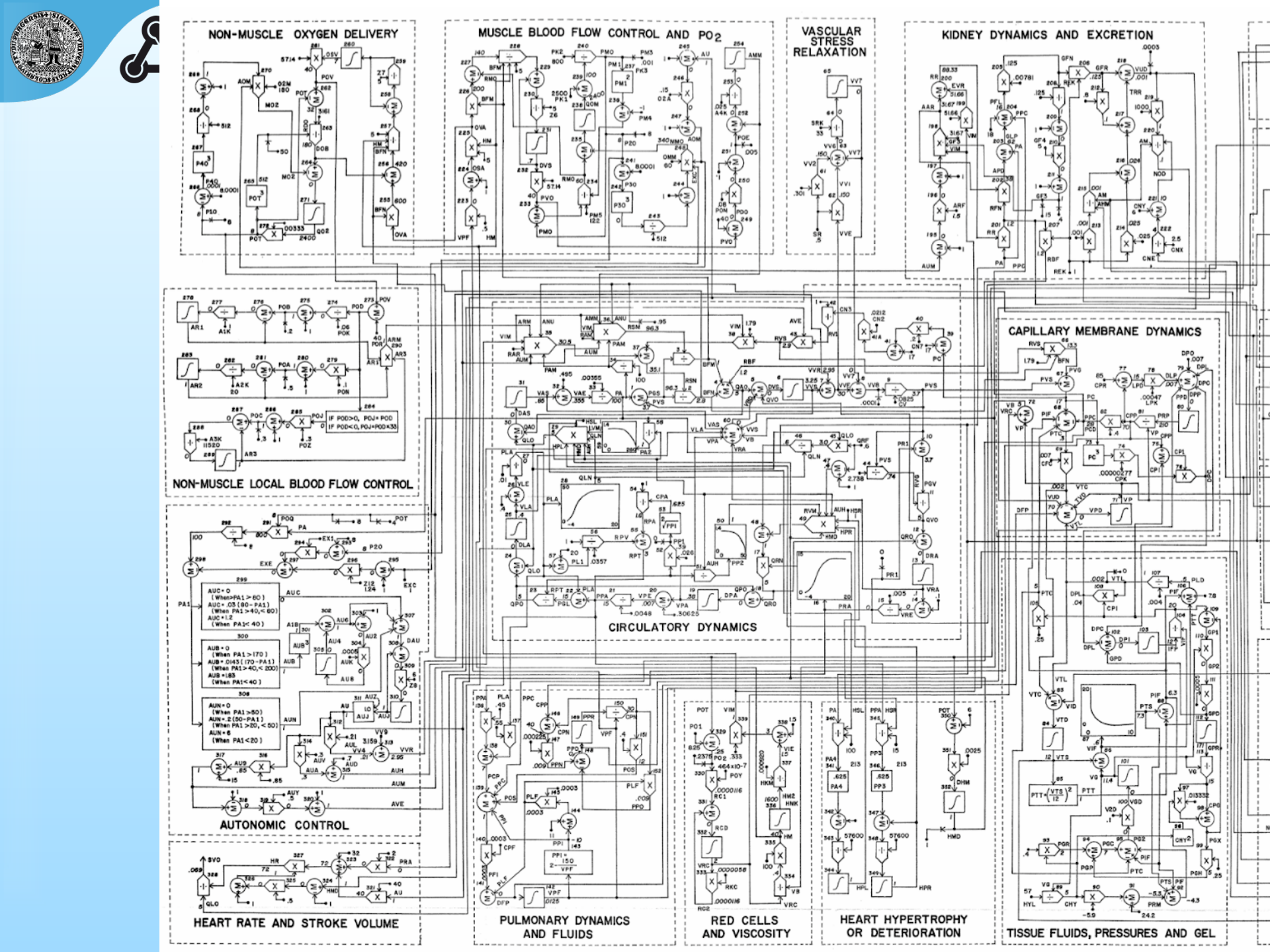
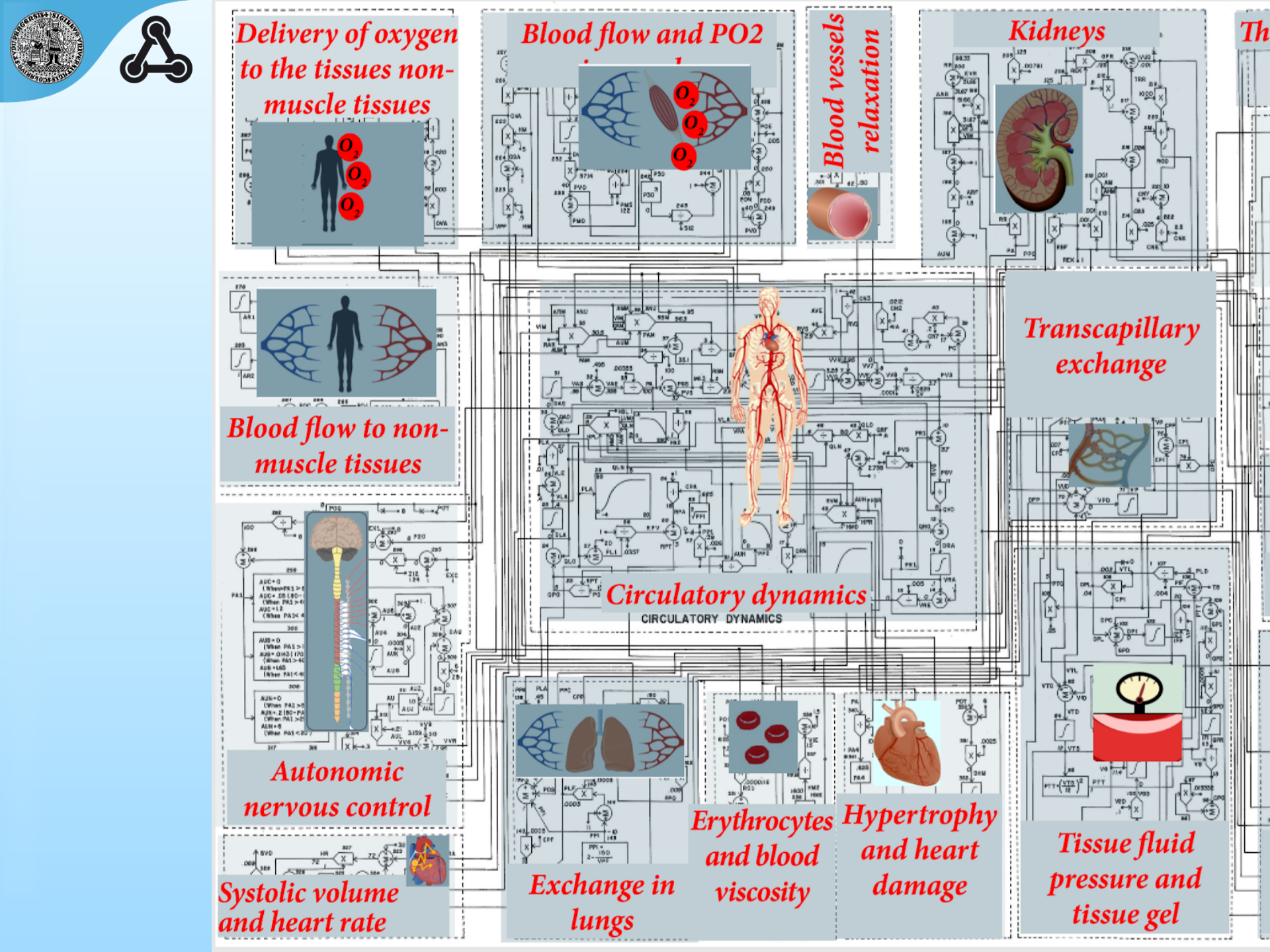
The origin - a web of physiological regulations

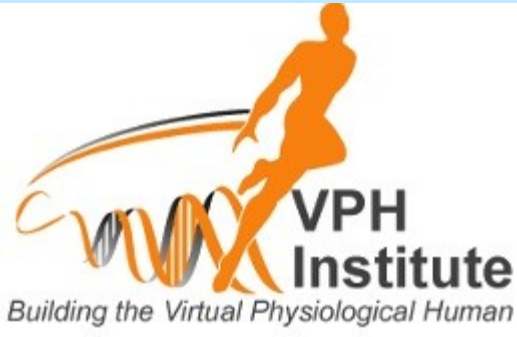
- A famous article by Arthur Guyton (1972)
- started an era of integrative physiology
- A new way how to view physiology
  - quantification
  - formalization

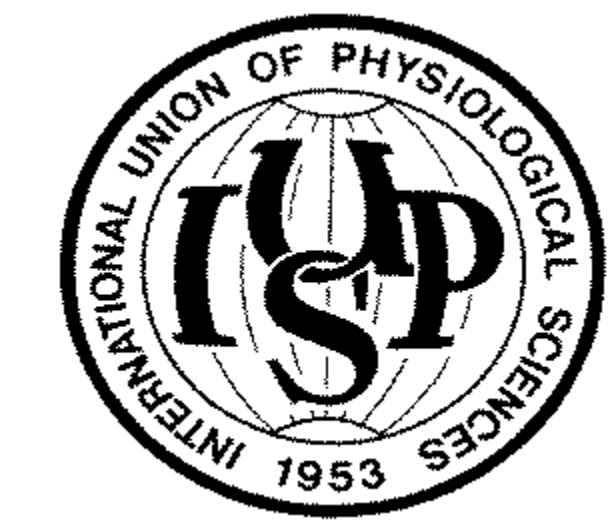

NON-MUSCLE OXYGEN DELIVERY
MUSCLE BLOOD FLOW CONTROL AND PO_2
VASCULAR STRESS RELAXATION
KIDNEY DYNAMICS AND EXCRETION
NON-MUSCLE LOCAL BLOOD FLOW CONTROL
CIRCULATORY DYNAMICS
CAPILLARY MEMBRANE DYNAMICS
AUTONOMIC CONTROL
HEART RATE AND STROKE VOLUME
PULMONARY DYNAMICS AND FLUIDS
RED CELLS AND VISCOSITY
HEART HYPERTROPHY OR DETERIORATION
TISSUE FLUIDS, PRESSURES AND GEL


Delivery of oxygen to the tissues non-muscle tissues
Blood flow and PO2
Blood vessels relaxation
Kidneys
Blood flow to non-muscle tissues
Transcapillary exchange
Circulatory dynamics
CIRCULATORY DYNAMICS
Autonomic nervous control
Systolic volume and heart rate
Exchange in lungs
Erythrocytes and blood viscosity
Hypertrophy and heart damage
Tissue fluid pressure and tissue gel

Formalization of physiological relations

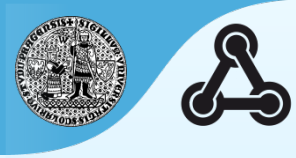
- Physiome project
- in EU: IUPS Physiome
- In USA: e.g. the Virtual RAT
- … lot of research attention





Model re-implementation: our experience

- Reproducibility - the main approach in exploring the nature
  - often violated though
- around 80 % of models implemented based on a description contain some error, that prevents from using the model correctly



Model re-implementation: our experience

- minor mistake of the authors (e.g. index, value unit etc..) -> unreproducible
- versioning problem
  - published version is older than the obtained
- The peer-review problem
  - not reimplemented by the reviewers
  - not even run by the reviewers

Model presentation in scientific publications

- graphical diagram is not enough
- equations are not enough

- too complex to show all equations, parameters and initial values

Model presentation in scientific publications

- Therefore, a paper MUST be accompanied with a digital appendix
  - model structure
  - parameters
  - starting values

Modeling paper's supplement

- preferably with a **source code** in a common, formal, programming language
- Versioning
  - field- or institution- specific open access repositories
  - general open-access repository, e.g. Zenodo, OpenDepot, or GitHub.

- This is becoming a standard, especially in a number of open-access journals

Biomedical models repositories

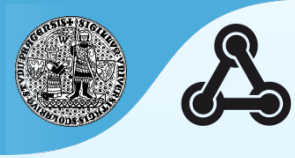
- Efforts of the Physiome project
- often dedicated to a specialized language of its own
- open languages and free tools

Biomedical model tools

- Virtual Cell project (http://vcell.org) - visualization and simulation of the cell metabolism and cell signal paths
  - client-server environment
- "Bio Tapestry" (http://www.biotapestry.org) - modeling regulatory gene networks
- JSim (http://www.physiome.org/jsim) - general extensive database of physiological models, JSim is a java-based, specialized modeling language
- CellML (http://www.cellml.org) - a general MathML-based modeling language, a large database of physiological models created in CellML are available at: https://models.physiomeproject.org

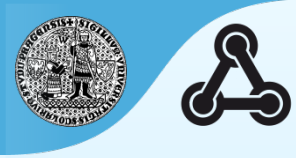
Biomedical models tools

- mostly causal, block-oriented languages.
  - including Matlab/Simulink
- User must develop the computation process
  - but e.g. SimScape, further tool development
  - The development of specialized simulation tools is limited by the funding allocated for the physiological research.



UNDERSTANDABLE MODEL

for both author and reader



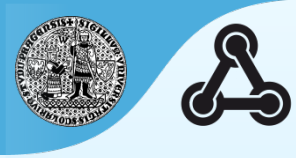
New modeling environments

Fortran

-> Simulink

-> ...

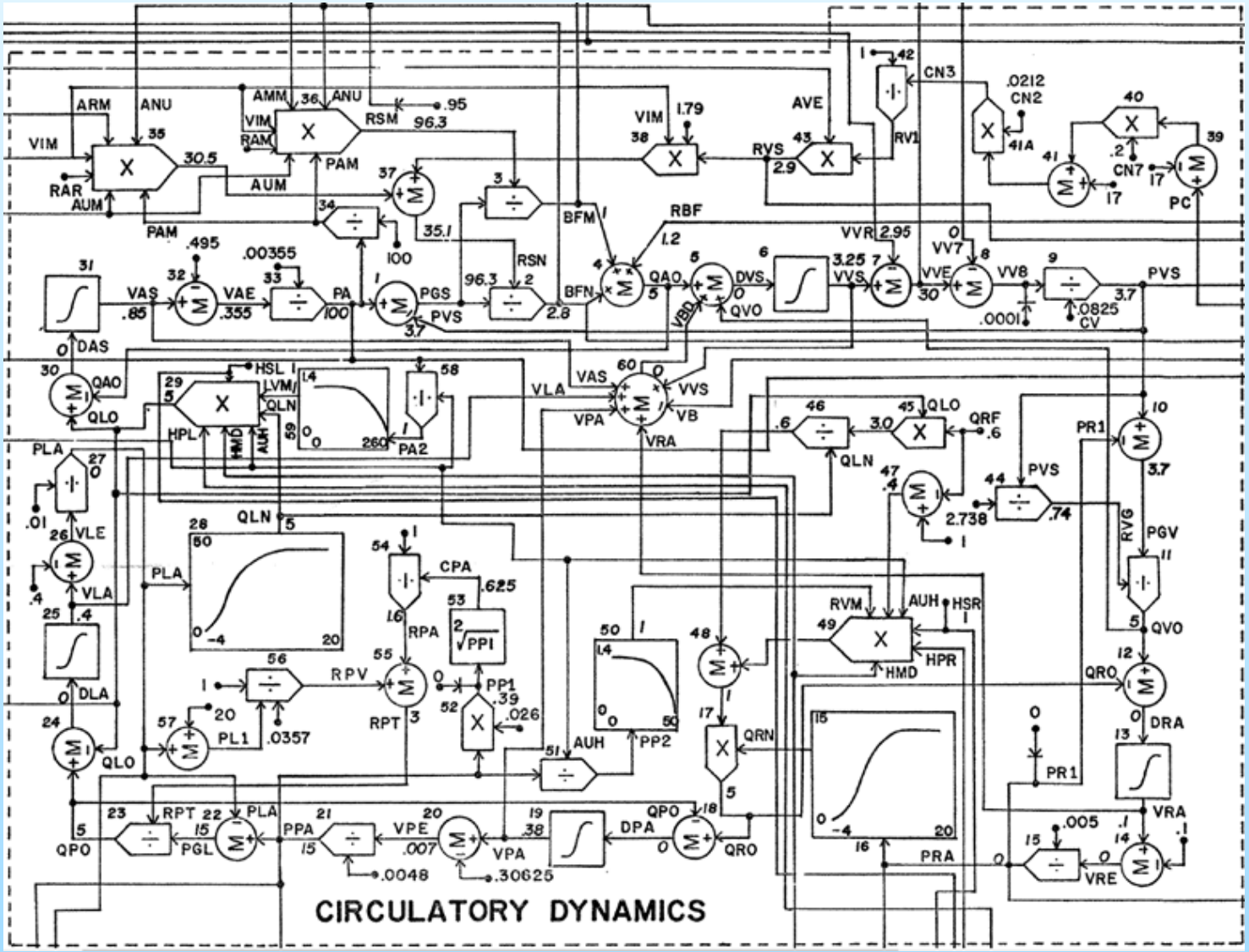
-> Modelica?



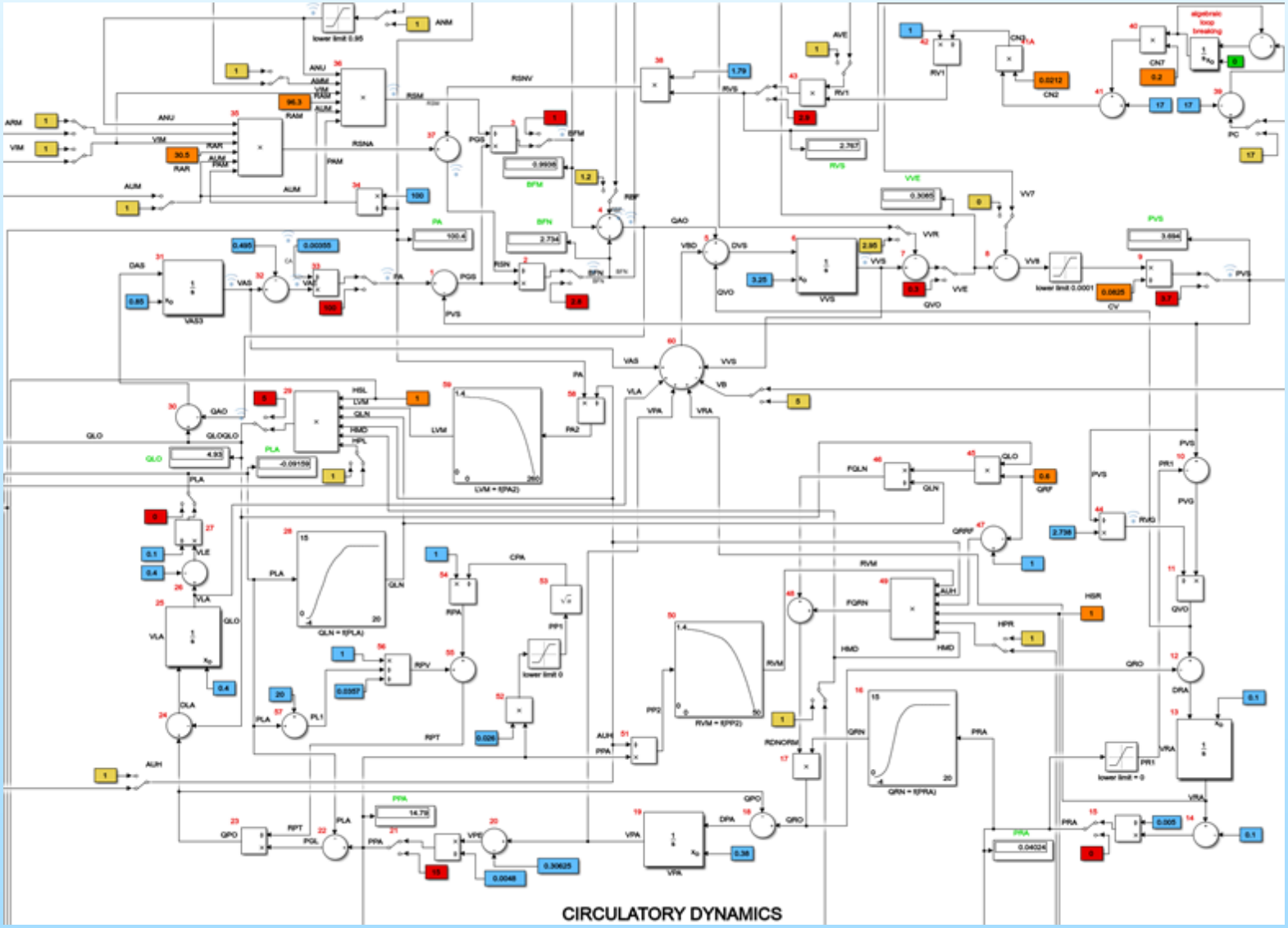
G72 – Fortran source

```
CIRCULATORY DYNAMICS BLOCK
C     HEMODYNAMICS
VBD=VP+VRC-VVS-VAS-VLA-VPA-VRA
VVS=VVS+DVS*I2+VBD*0.3986
VPA=VPA+DPA*I2+VBD*0.155
VAS=VAS+DAS*I2+VBD*0.261
VLA=VLA+DLA*I2+VBD*0.128
VRA=VRA+DRA*I2+VBD*0.0574
VAE=VAS-0.495
PA=VAE/0.00355
PAM=100./PA
PA2=PA/AUH
CALL FUNCTN(PA2,LVM,FUN1)
VRE=VRA-0.1
PRA=VRE/0.005
CALL FUNCTN(PRA,QRN,FUN2)
VPE=VPA-0.30625
PPA=VPE/0.0048
PP1=0.026*PPA
IF(PP1.LT.0.)PP1=0.
RPA=PP1**(-0.5)
PP2=PPA/AUH
CALL FUNCTN(PP2,RVM,FUN3)
VLE=VLA-0.4
PLA=VLE/0.01
CALL FUNCTN(PLA,QLN,FUN4)
RPV=1./(PLA+20.)/0.0357
RPT=RPV+RPA
PGL=PPA-PLA
QPO=PGL/RPT
ANU=ANM
IF(ANU.LT.0.8)ANU=0.8
VVE=VVS-VVR-(ANU-1.)*ANY
VV8=VVE-VV7
IF(VV8.LT.0.0001)VV8=0.0001
PVS=VV8/CV
PR1=PRA
IF(PRA.LT.0.)PR1=0.
RVG=2.738/PVS
QVO=(PVS-PR1)/RVG
CN3=CN3+(((PC-17.)*CN7+17.)*CN2-CN3)*0.1
AVE=(AUM-1.)*AUY+1.
RVS=AVE*(1./CN3)*VIM*((ANU-1.)*ANZ+1.)
PGS=PA-PVS
RSN=RAR*ARM*ANU*AUM*PAM*VIM+RVS*1.79
BFN=PGS/RSN
RSM=ANU*VIM*PAM*AUM*AMM*RAM
BFM=PGS/RSM
QAO=BFN+BFM+RBF+(PA-PRA)*FIS
QLO=LVM*QLN*AUH*HSL*HMD*HPL
QRO=QRN*((1.-QRF)*AUH*RVM*HSR*HMD*HPR+QRF*QLO/QLN)
QPO=QLO+(QPO-QLO)/U
QVO=QRO+(QVO-QRO)/X
DVS=QAO-QVO
DPA=QRO-QPO
DAS=QLO-QAO
DLA=QPO-QLO
DRA=QVO-QRO
```

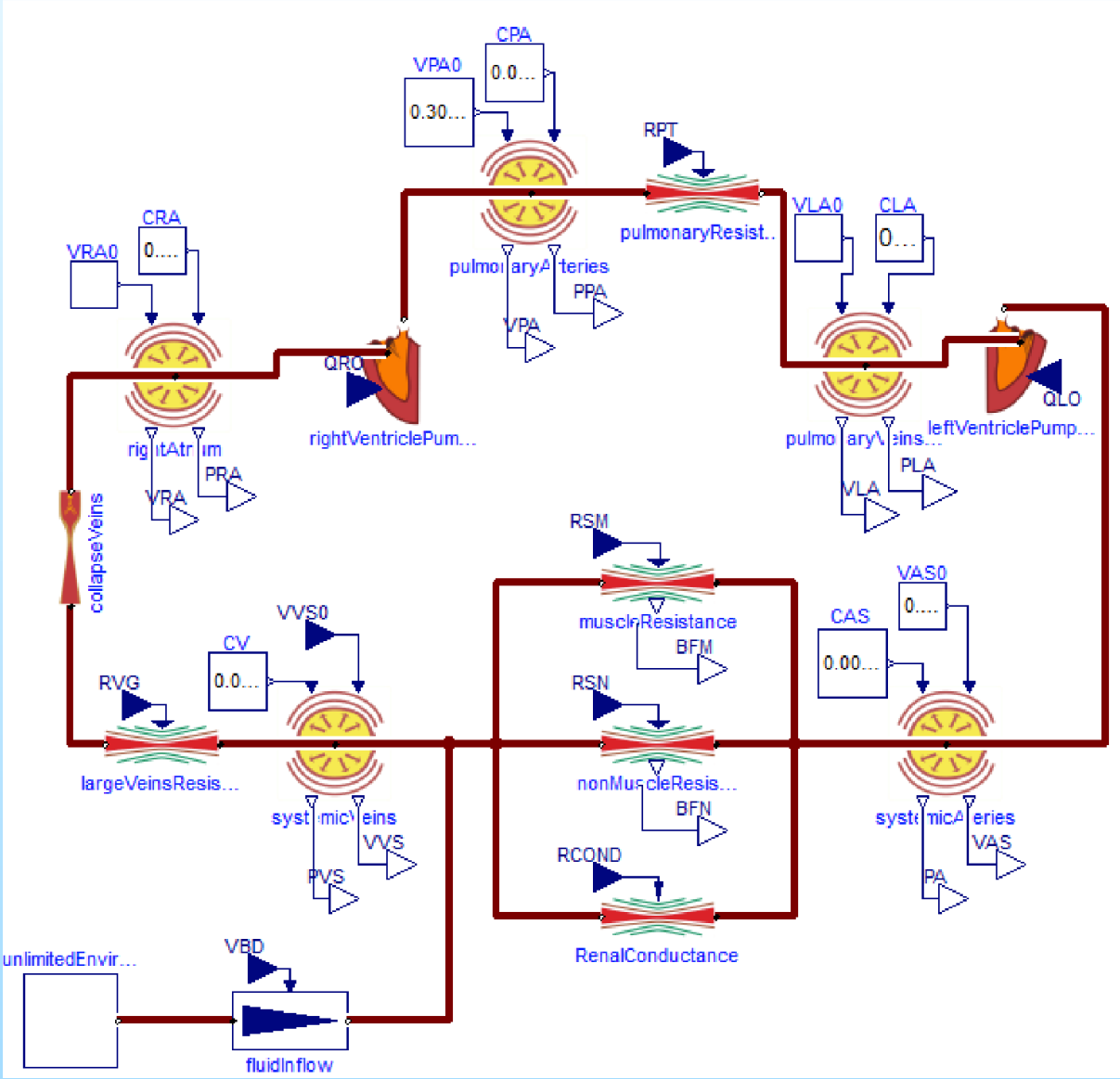
G72 circulation – the schematics



G72 circulation – Simulink



G72 circulation - Modelica

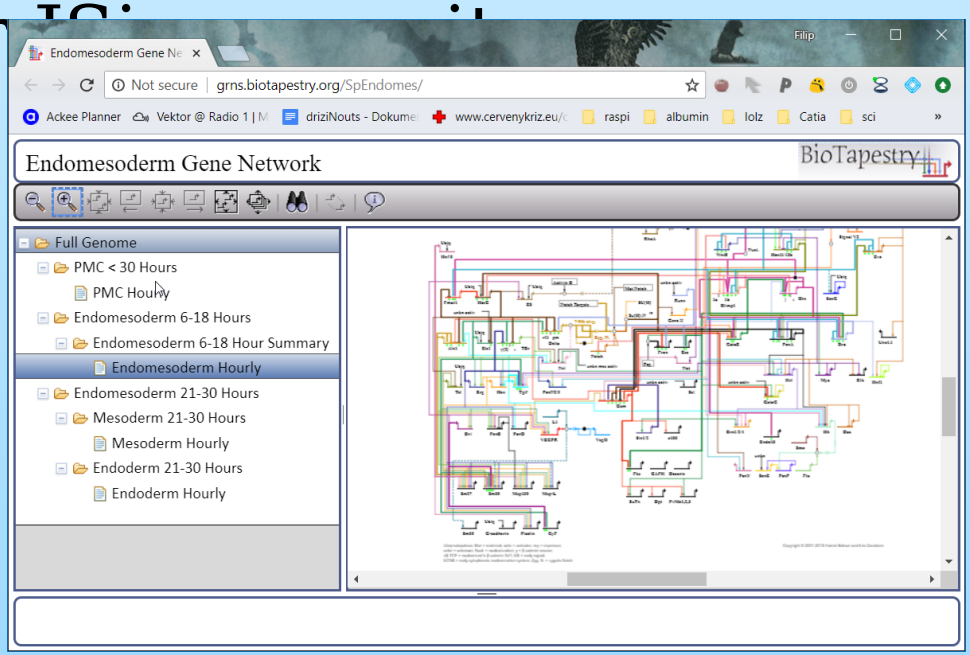


Modelica unifies all advantages

- open language, free tools
- equation-based
- visual, understandable model design
- includes documentation
- powerful solvers
- tool development funded by rich industries

Still, two drawbacks

1. web-based presentation
   - such as BioTapestry
2. specific libraries, model repositories
   - such as CellML or IS

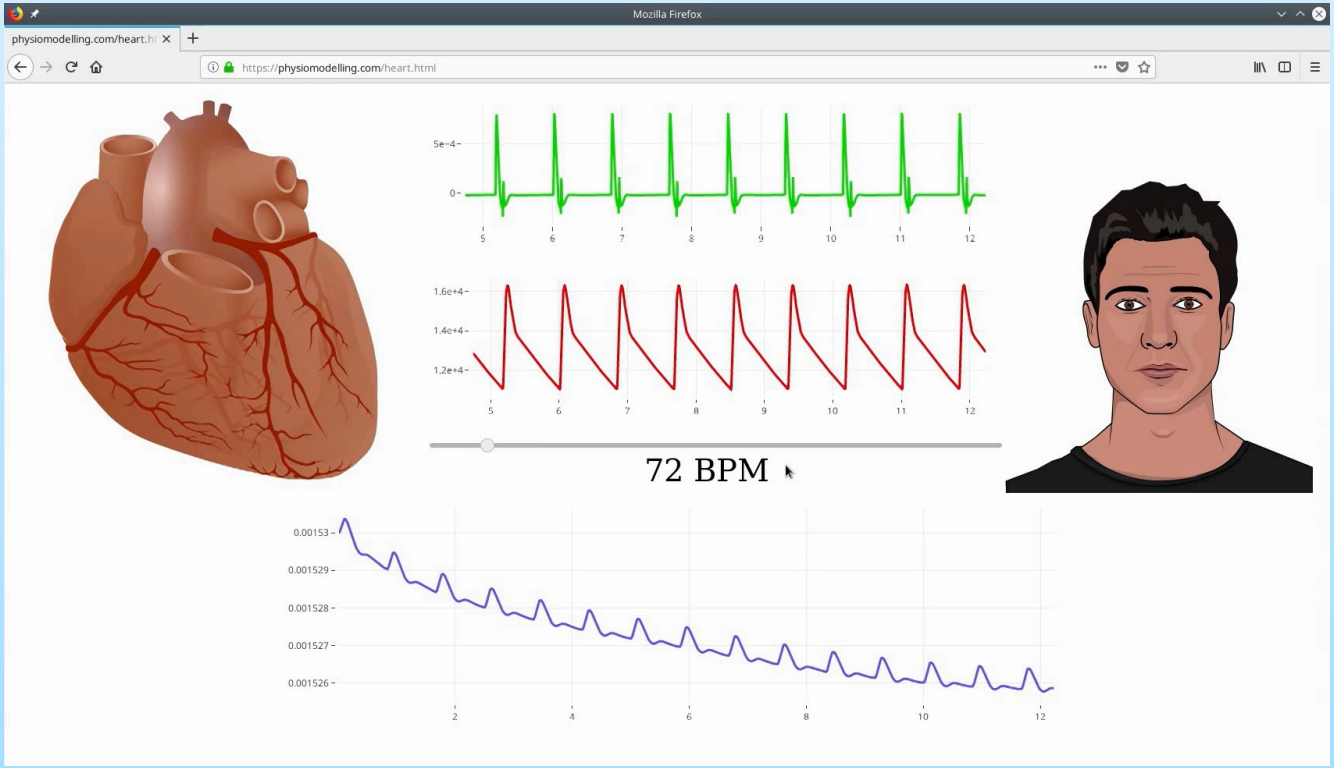


1. Bodylight.js

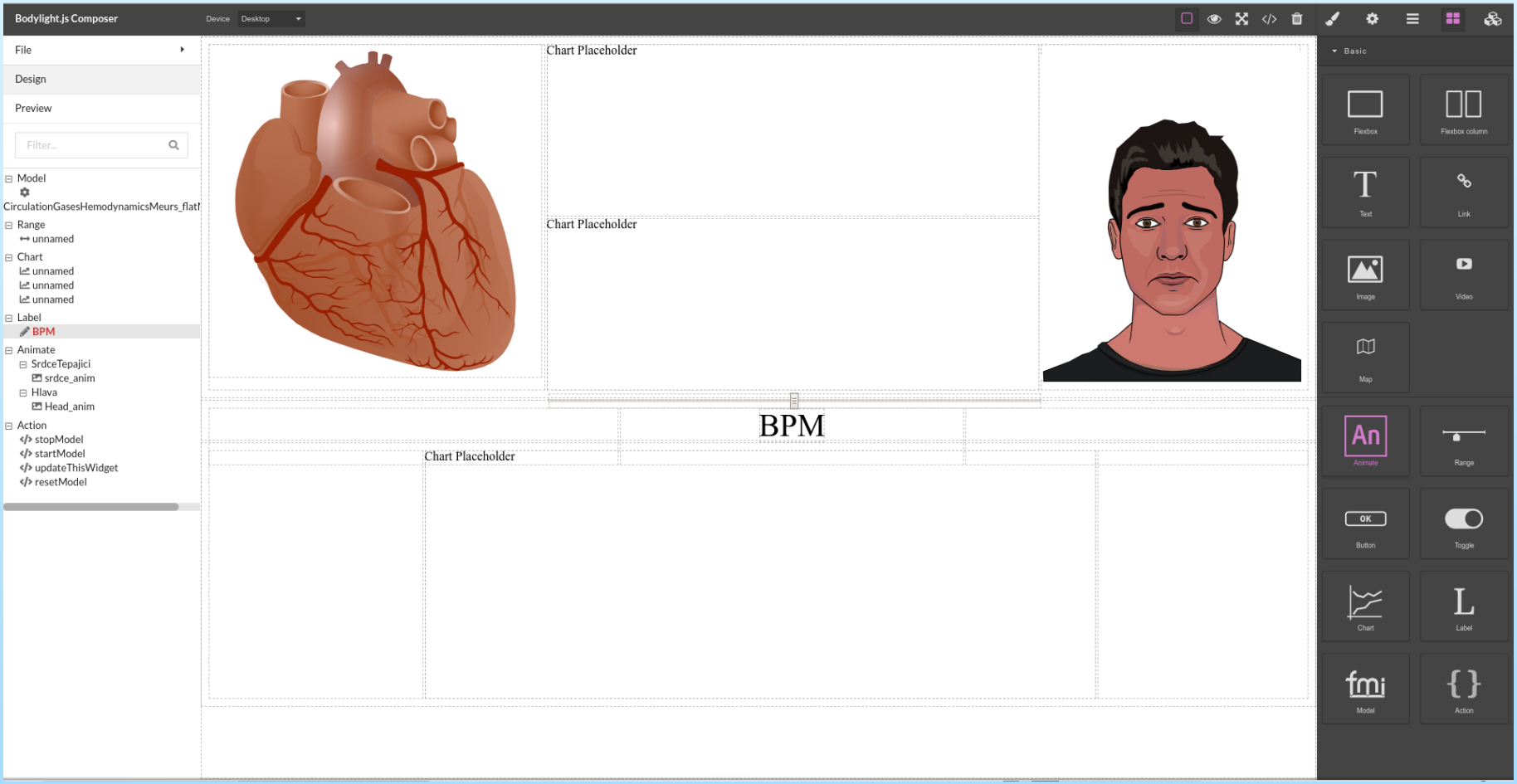
- FMU-based toolchain for web-simulator development
- pure client-side application
  - model is in binary (webassembly)
  - FMU 2.0 co-simulation, incl. sources
    - (Only Dymola at the moment, ticket #4273 in OM)
  - emscripten JavaScript translation + model controls + graphs + animation components

1. Bodylight.js

- https://physiomodelling.com/circulation/

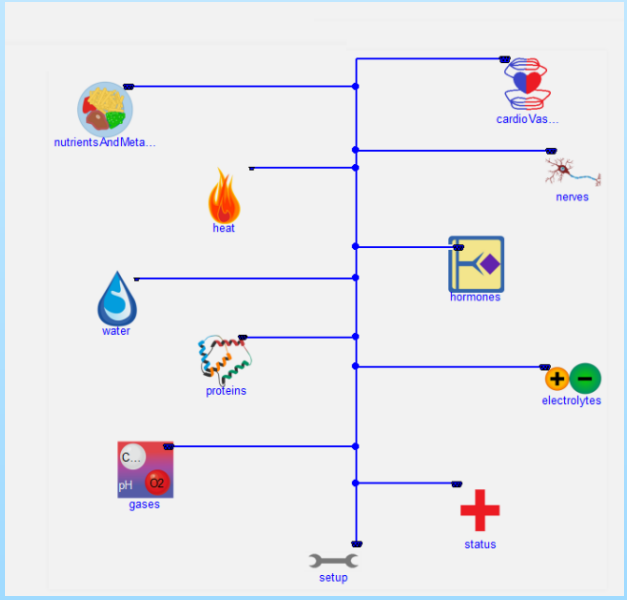


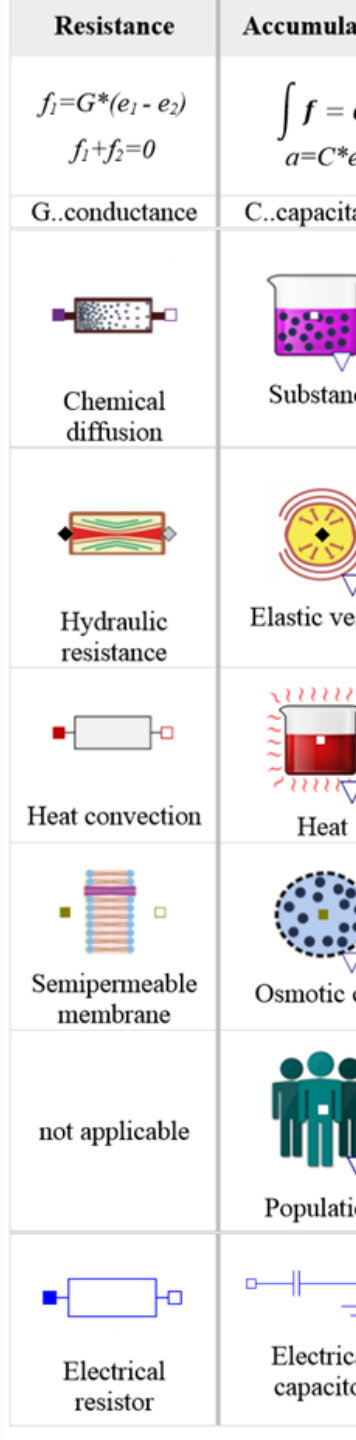
Bodylight.js-composer



2. Physiolibrary

- proved on Physiomodel, our Modelica reimplementation of the largest physiological model, the Hummod





2. Community is an important factor

- feedback ensures further innovation

  open scientific development
  +
  business opportunities and financing

  - Medical education, simulators
  - Pharmacology
  - R&D

Thus..

- following the example of the *Open Source Modelica Consortium ...*
- ***Physiomodeling*** *Open Source Consortium* ?
- www.PhysioModelling.com