Collège de France

Pr Nicholas Ayache Symposium

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Computational Physiology: Connecting molecular systems biology with clinical medicine

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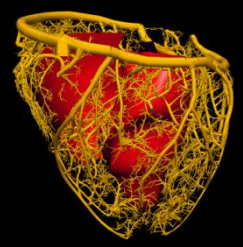
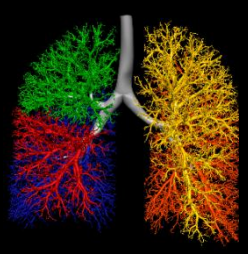
NEW ZEALAND

Part 1

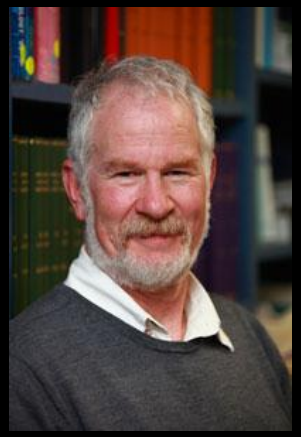
Examples (from the ABI):

1. Circulatory system: Heart
2. Respiratory system: Lungs
3. Musculo-skeletal system
4. Digestive system: Stomach
5. Brain & facial muscles





1. **Circulatory system**
2. **Respiratory system**
3. **Musculo-skeletal system**
4. **Digestive system**
5. **Brain & facial muscles**



Bruce Smaill

Martyn Nash

Alistair Young

Cardiac team

Peter Hunter
Ian LeGrice
Denis Loiselle
Martyn Nash
Greg Sands
Bruce Smaill
Nic Smith
Andrew Taberner
Alistair Young
Jichao Zhao
Jesse Ashton

Heart physiome: Multi-physics and multi-scale

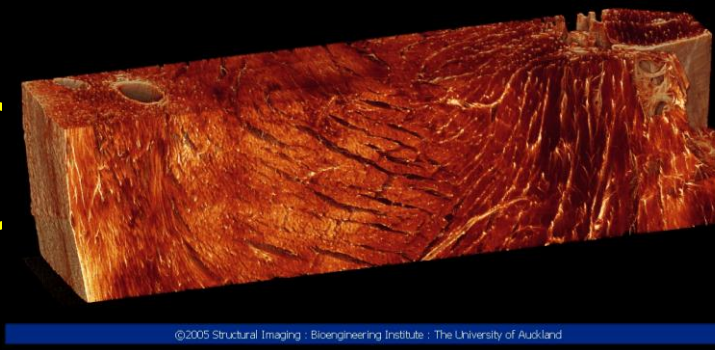
m
$=10^9$nm

nm

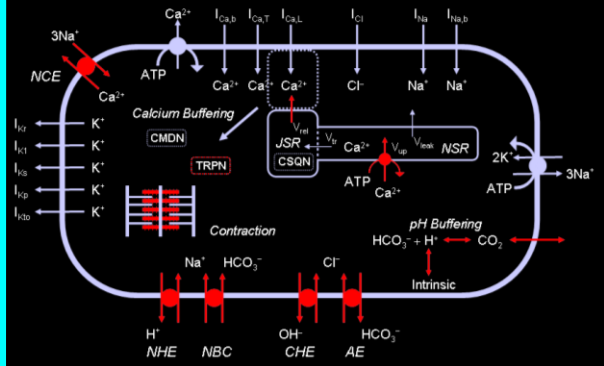
torso

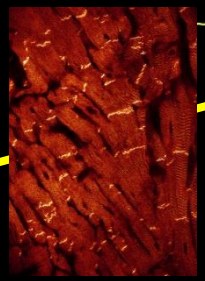
heart

tissue



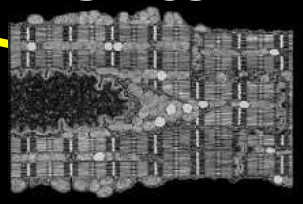
cellular processes



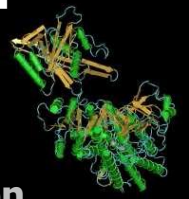


cell-cell connections

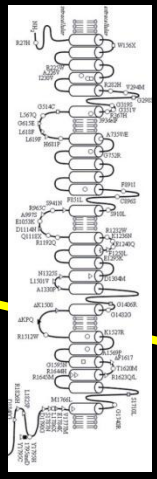
3D cell



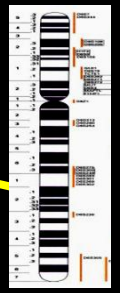
proteins



amino acid sequence



genomic sequence



Hunter PJ, Pullan AJ, Smaill, BH. Modeling total heart function. *Annual Review of Biomedical Engineering*, 5:147-177, 2003
LeGrice IJ, Hunter PJ, Smaill BH. *Am.J.Physiol.* 272:H2466-H2476, 1997

Torso model

Organ model

Myocardial activation
Ventricular wall mechanics
Ventricular blood flow
Heart valve mechanics
Coronary blood flow
Neural control

Continuum tissue model

Discrete tissue structure model

Calcium transport models
Myofilament mechanics
Signal pathway models
Metabolic pathway models
Gene regulation models

Composite lumped parameter cell model

Hodgkin-Huxley type ion channel model

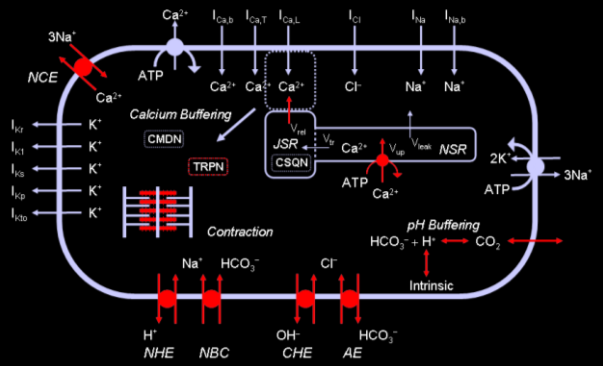
Markov ion channel model

3D protein model

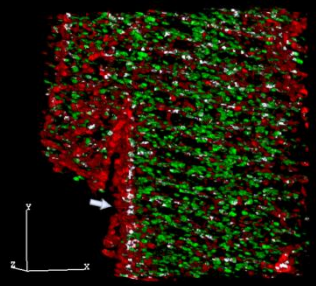
Coarse grained MD model

Molecular dynamics model

Quantum mechanics model



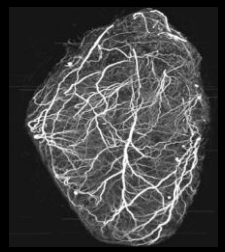
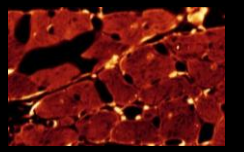
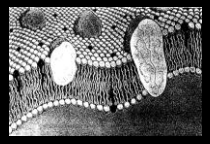
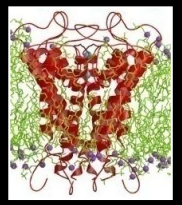
3D cell model



Scale Imaging Multi-scale Modelling

Organism
Organ system
Organ
Tissue
Cell
Network
Protein
Gene
Atom

1m
10^{-3}
10^{-6}
10^{-9}

Partial differential equations (PDEs)

Reaction-diffusion

$$\frac{\partial C}{\partial t} + \boldsymbol{u}.\nabla C = -\nabla.(-k\nabla C) + f_s$$

Fluid flow

$$\frac{\partial \boldsymbol{u}}{\partial t} + \boldsymbol{u}.\nabla \boldsymbol{u} = -\frac{1}{\rho}\nabla p + \upsilon\nabla^2\boldsymbol{u}$$

Finite elasticity

$$\tau^{ij}\big|_i = f^j \qquad \tau^{ij} = f(e_{ij})$$

$$e_{ij} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} + \frac{\partial u_k}{\partial x_i}\cdot\frac{\partial u_k}{\partial x_j}\right)$$

Electro-magnetic

$$\nabla.\boldsymbol{E} = \frac{\rho}{\epsilon} \qquad \nabla x\boldsymbol{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

$$\nabla.\boldsymbol{B} = 0 \qquad \nabla x\boldsymbol{B} = \mu\left(\boldsymbol{J} + \epsilon\frac{\partial \mathbf{E}}{\partial t}\right)$$

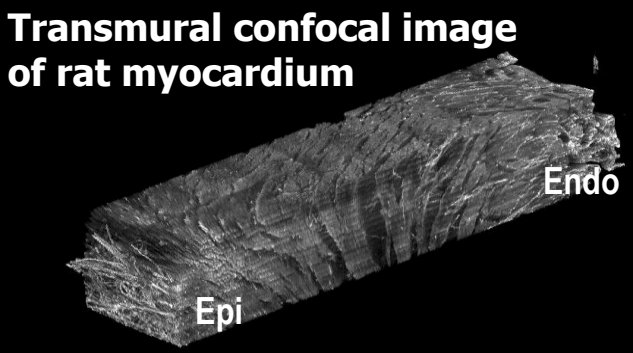
Differential algebraic equations

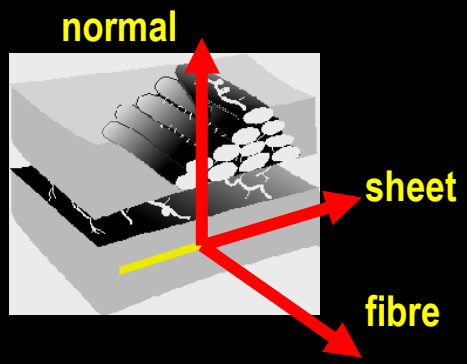
Bayesian network description

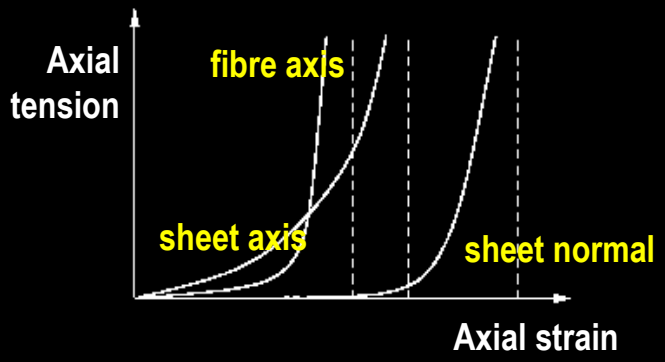
Molecular dynamics/coarse graining

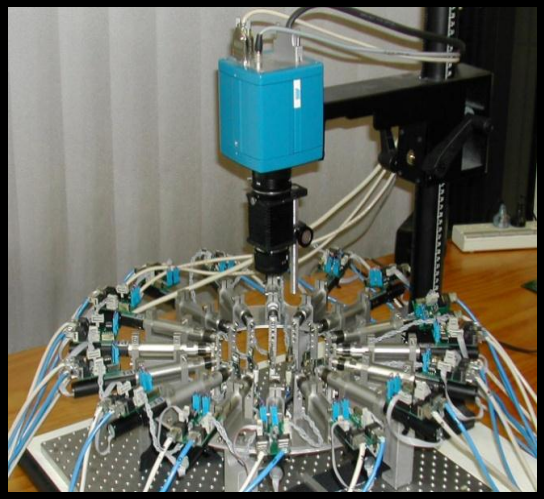
Poisson-Boltzmann …

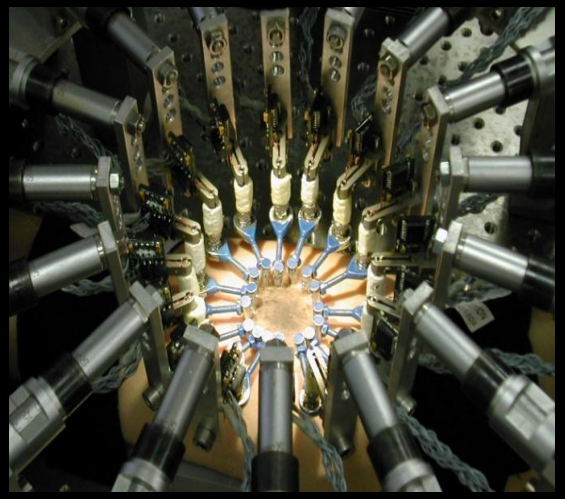
Tissue level function: passive properties

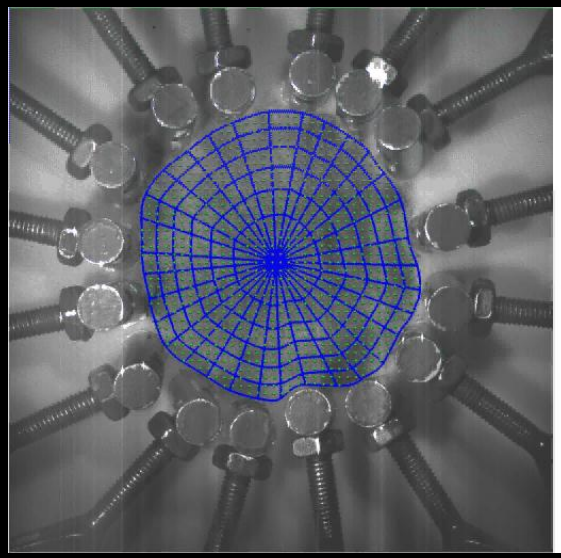


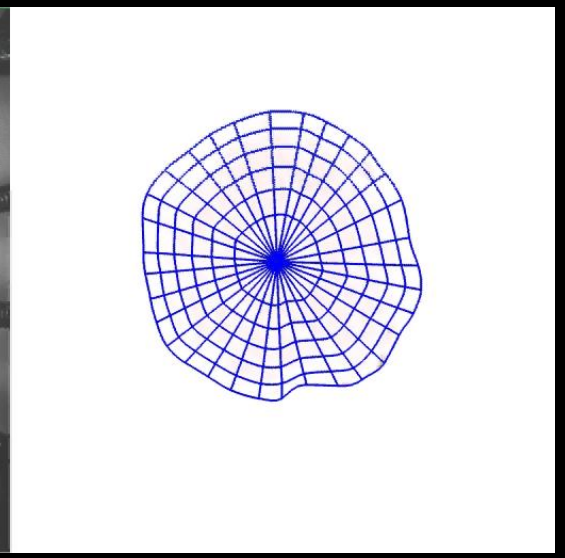






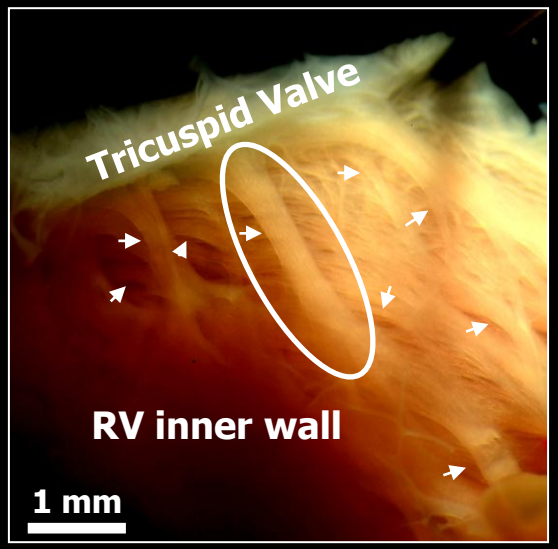






Hunter PJ, Smaill BH, Nielsen PMF. *Biophysical J,* 49(2):90a, 1986
Malcolm DTK, Nielsen PMF, Hunter PJ, Charette G. *BMMB*, 1(3):197-210, 2002
Schmid, H., Nash, M.P., Young, A.A., Röhrle, O., Hunter, P.J. *J Biomech Eng*, 129(2):279-283, 2007

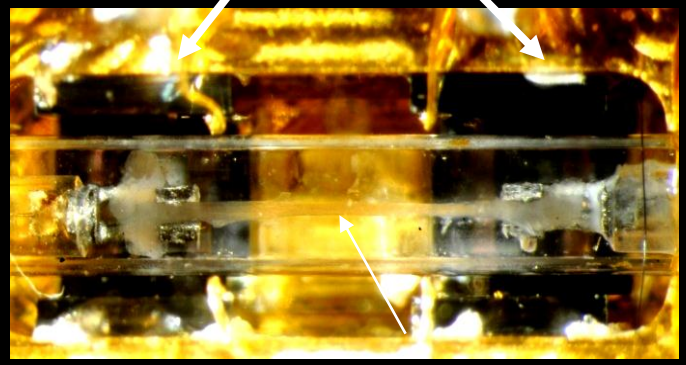
Tissue level function: active properties



Model:
- **electrophysiology**
- **myofilament mechanics**
- **metabolism**
- **signalling**

$$\frac{1 - T/T_0}{T/T_0 + a} = \sum_{i=1,3} A_i \int_{-\infty}^{t} e^{-\alpha_i (t-\tau)} \dot{\lambda}(\tau) d\tau$$

Thermopile arrays



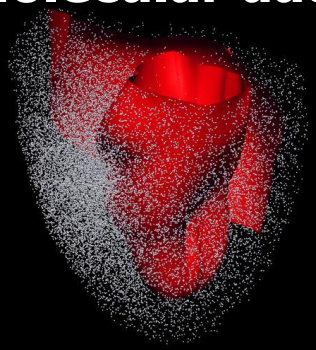
Hunter PJ, McCulloch AD & ter Keurs HEDJ. *Prog Biophys Molec Biol* 69:289-331, 1998
Niederer, S.A., Hunter, P.J., Smith, N.P. *Biophysical Journal*, 90(5):1697–1722, 2006

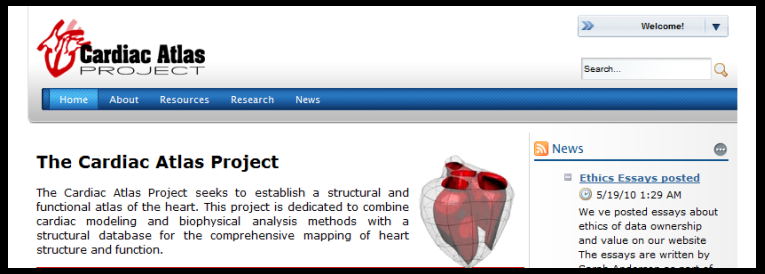
Model provides framework for aligning data

Radiological data

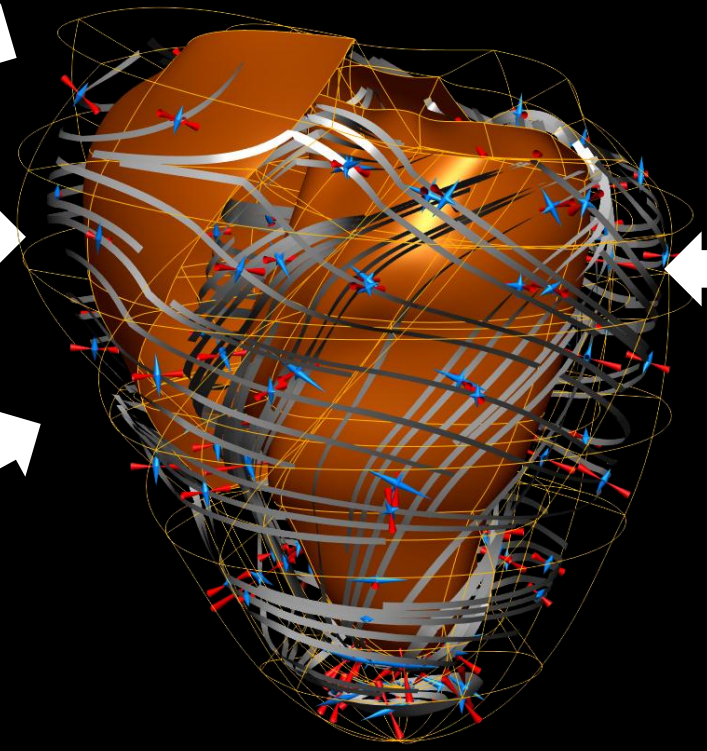
Structural data

Molecular data

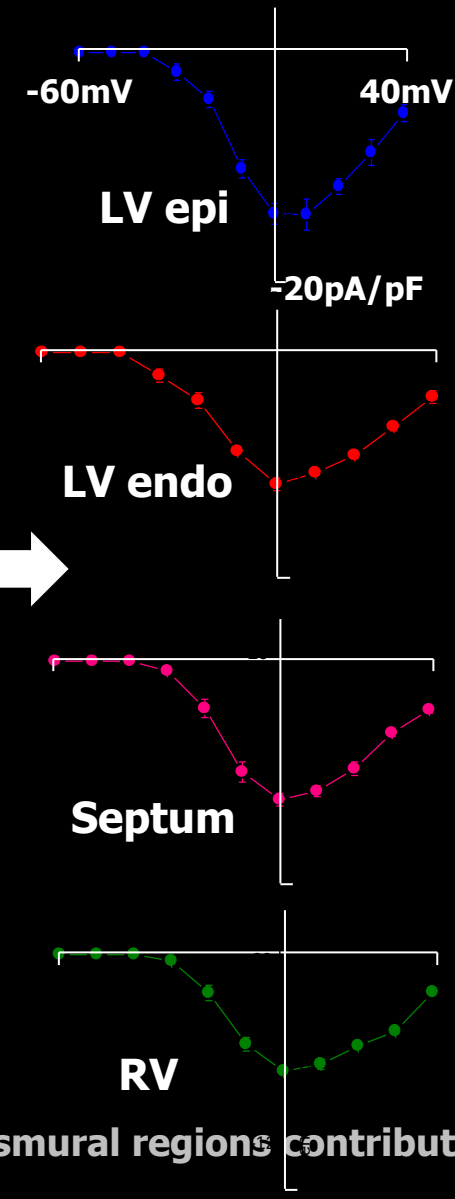




Mathematical model



Physiological data



Kim, Cannell & Hunter. Changes in calcium current among different transmural regions contributes to action potential heterogeneity in rat heart. *PBMB* 103(1):28-34, 2010

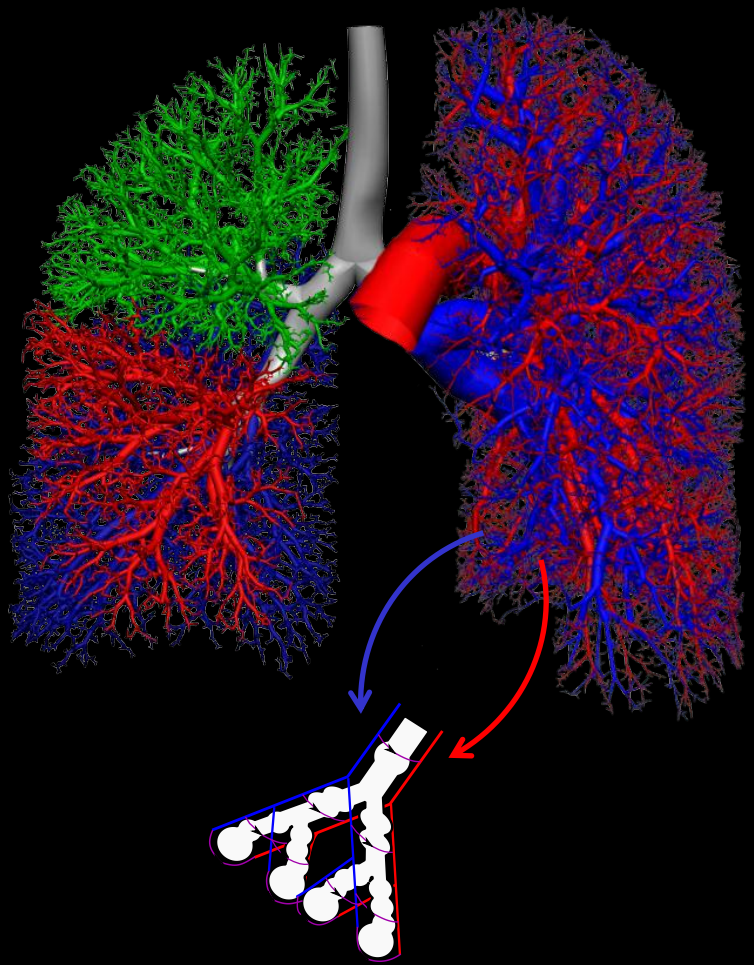
1. Circulatory system
2. **Respiratory system**
3. Musculo-skeletal system
4. Digestive system
5. Brain & facial muscles

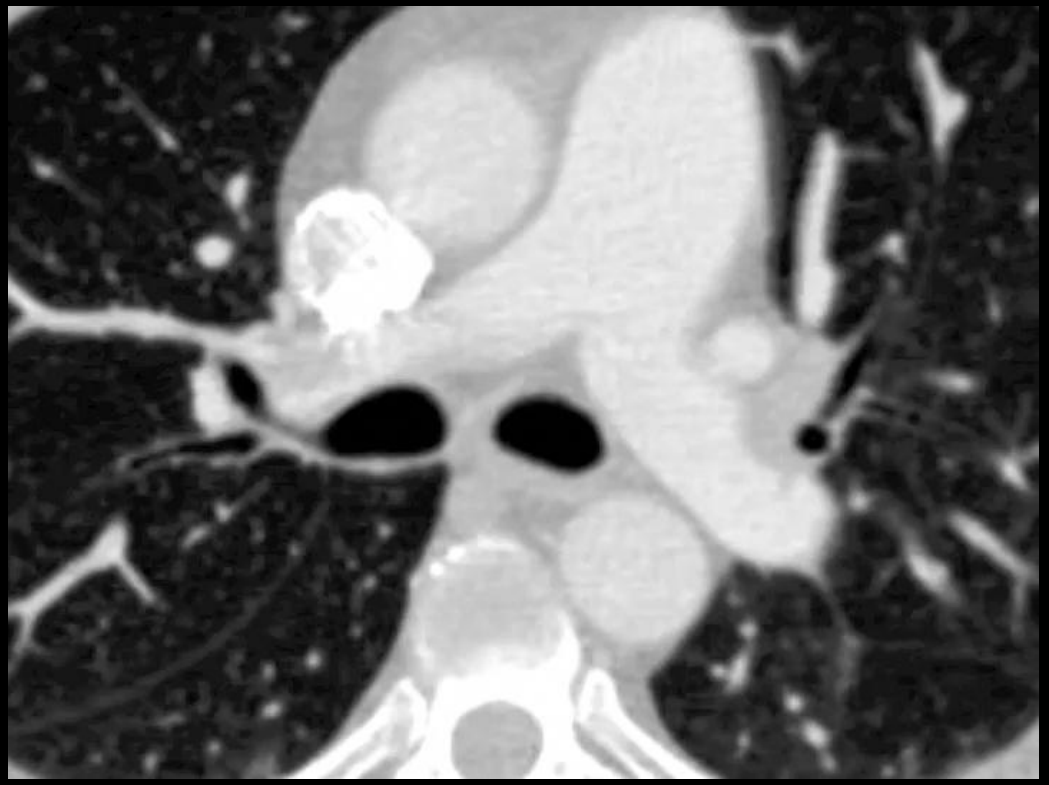
Lung team

Merryn Tawhai
Kelly Burrowes
Alys Clark
Hari Kumar
Barbara Breen
Kerry Hedges
Kelly Murphy
Josh Lee
Mabelle Lin
Karthik Subramaniam

Respiratory system

A multi-scale model of the lung





Tawhai MH, Clark AR, Donovan GM, Burrowes KS. Computational modeling of airway & pulmonary vascular structure & function: development of a `Lung Physiome'. *Critical Reviews in BME,* 2011.

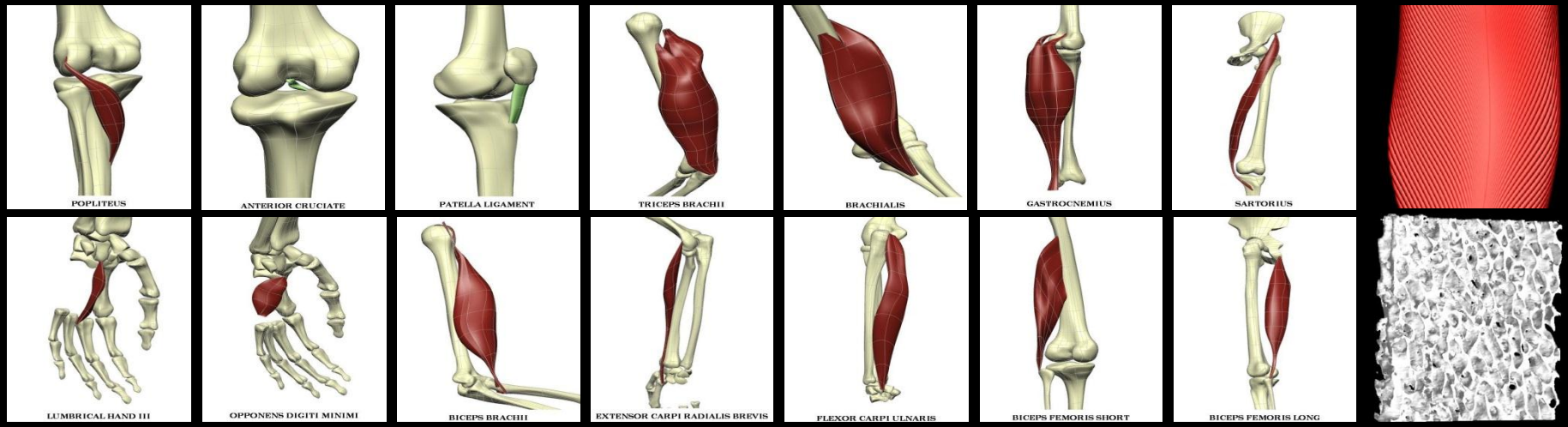
1. Circulatory system
2. Respiratory system
3. **Musculo-skeletal system**
4. Digestive system
5. Brain & facial muscles

Musculo-skeletal team

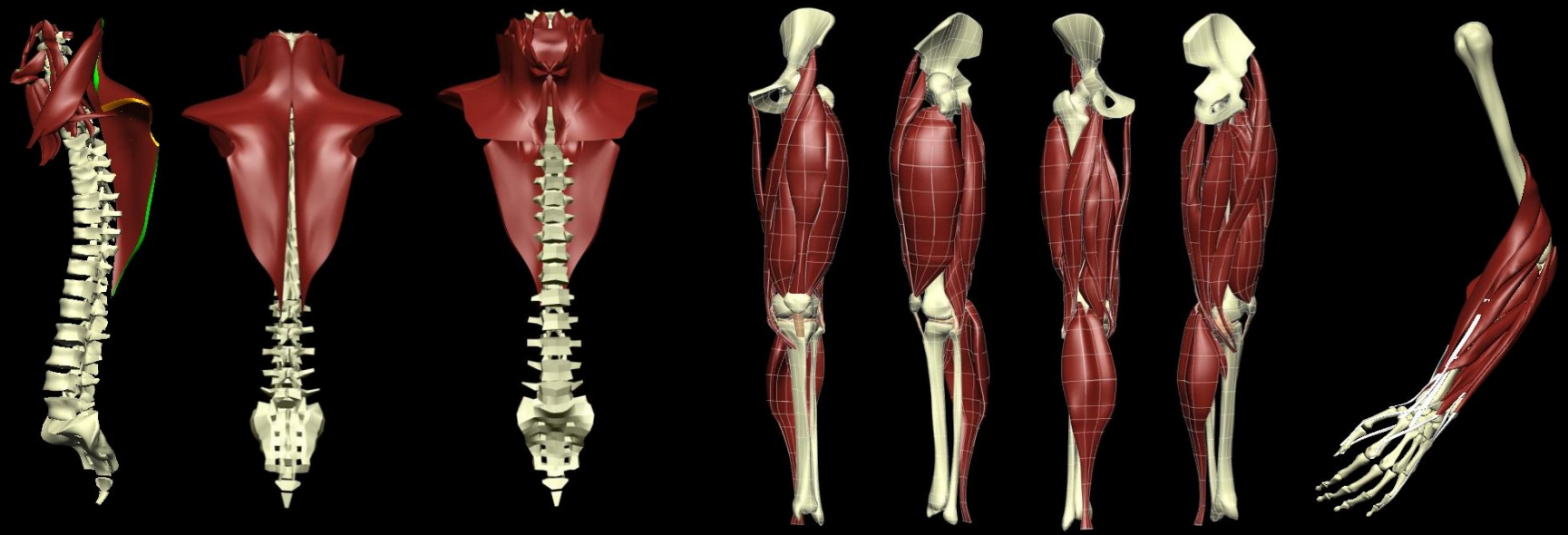
Thor Besier
Vickie Shim
Justin Fernandez
Peter Hunter
Poul Nielsen
Martyn Nash
Alice Hung
Jessica Jor
Duane Malcolm
Kumar Mithraratne
Mark Finch
Tim Wu
Yu Zhang

Musculo-skeletal system

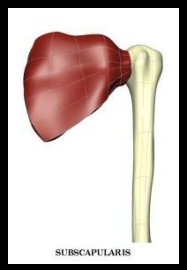
Web-accessible database of generic models (+ tissue structure):

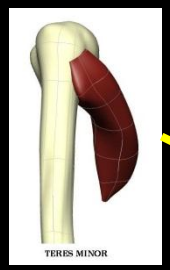


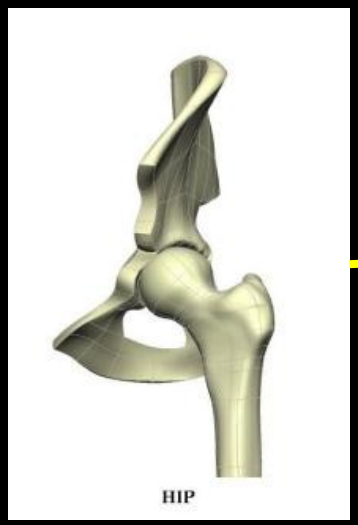
Load generic models into the anatomical component under study:

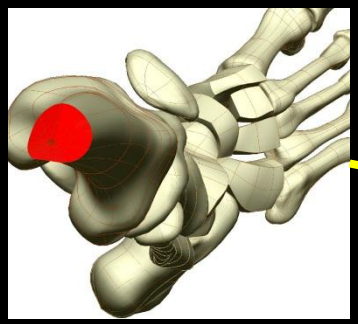


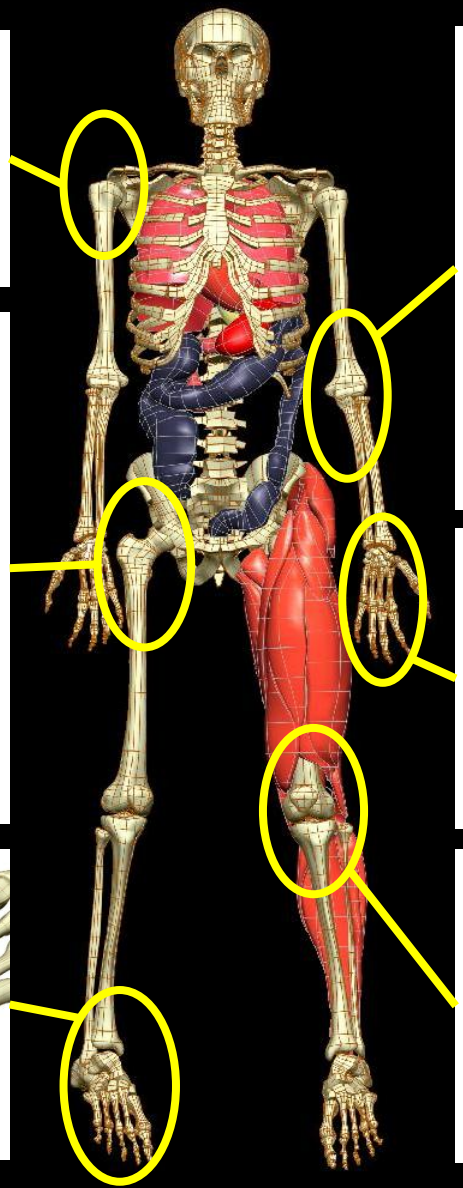
Generic models of the joints

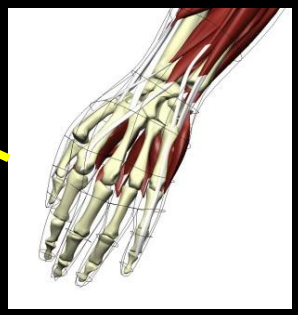


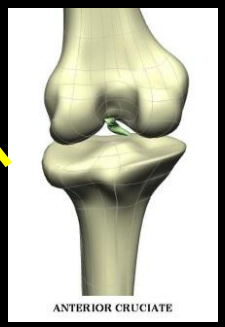








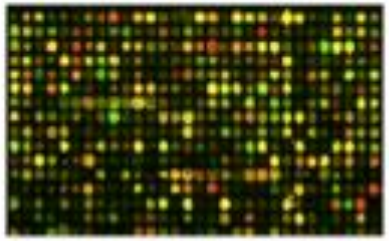




Shim VB, Hunter PJ, Pivonka P, Fernandez JW. A multiscale framework based on the physiome markup languages for exploring the initiation of osteoarthritis at the bone-cartilage interface. IEEE Trans Biomed Eng. 58(12):3532-6, 2011

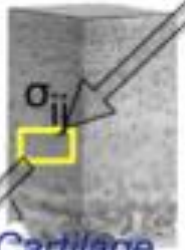
In vivo gene functions

In vivo joint loading



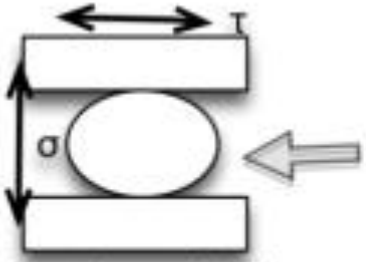
gene expressions of stimulated cells from the device

Knee FE model



Cartilage FE model

Chondrocyte FE model



Application of daily loading signals to cells with a novel device

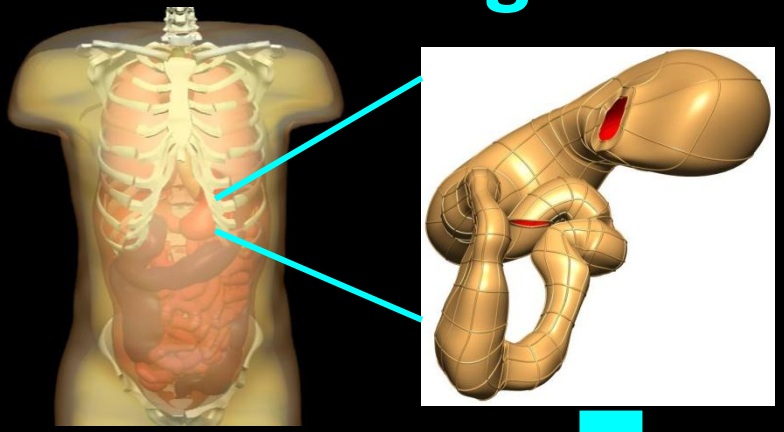
Multiscale knee model for modelling chondrocyte during daily activities

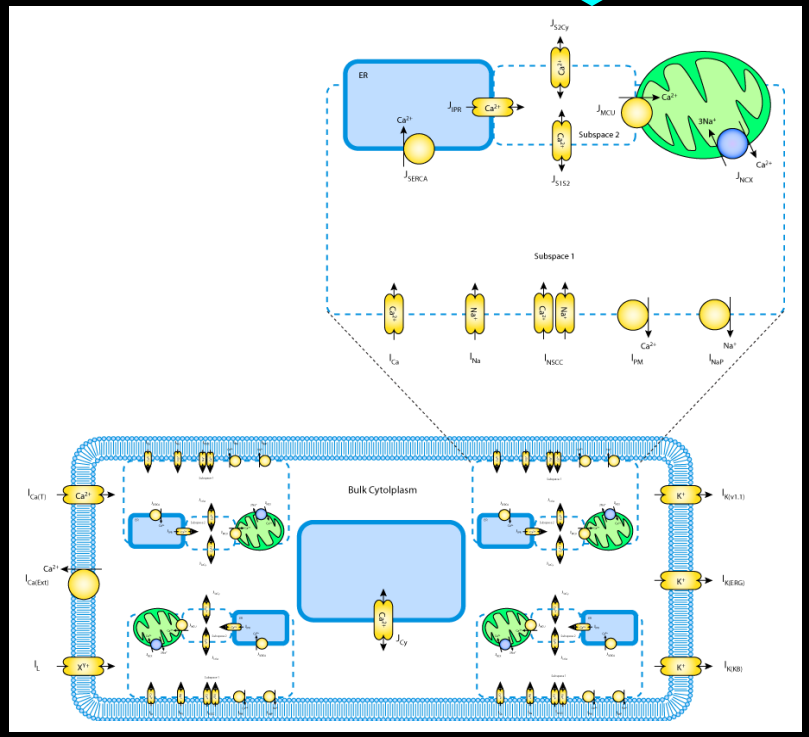
1. Circulatory system
2. Respiratory system
3. Musculo-skeletal system
4. **Digestive system**
5. Brain & facial muscles

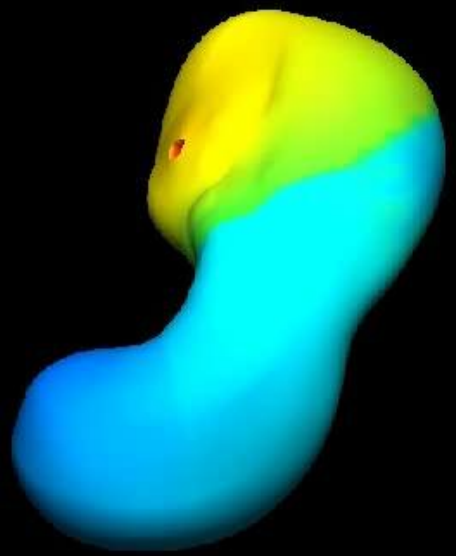
GI team

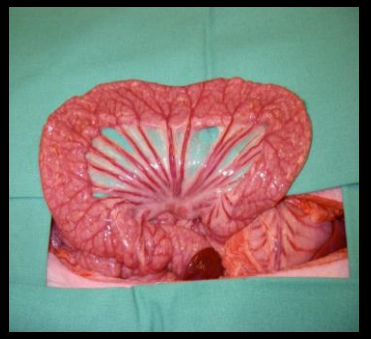
Andrew Pullan (1962-2012)
Leo Cheng
Peng Du
Greg O'Grady
Shawn Means
Tim Angeli
Jerry Gao
Rachel Lees-Green
Niranchan Paskaranandavadivel
Shameer Sathar
Binny Paul
Vinodh Vedachalam

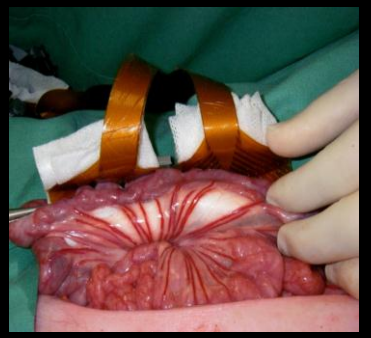
Digestive system: stomach









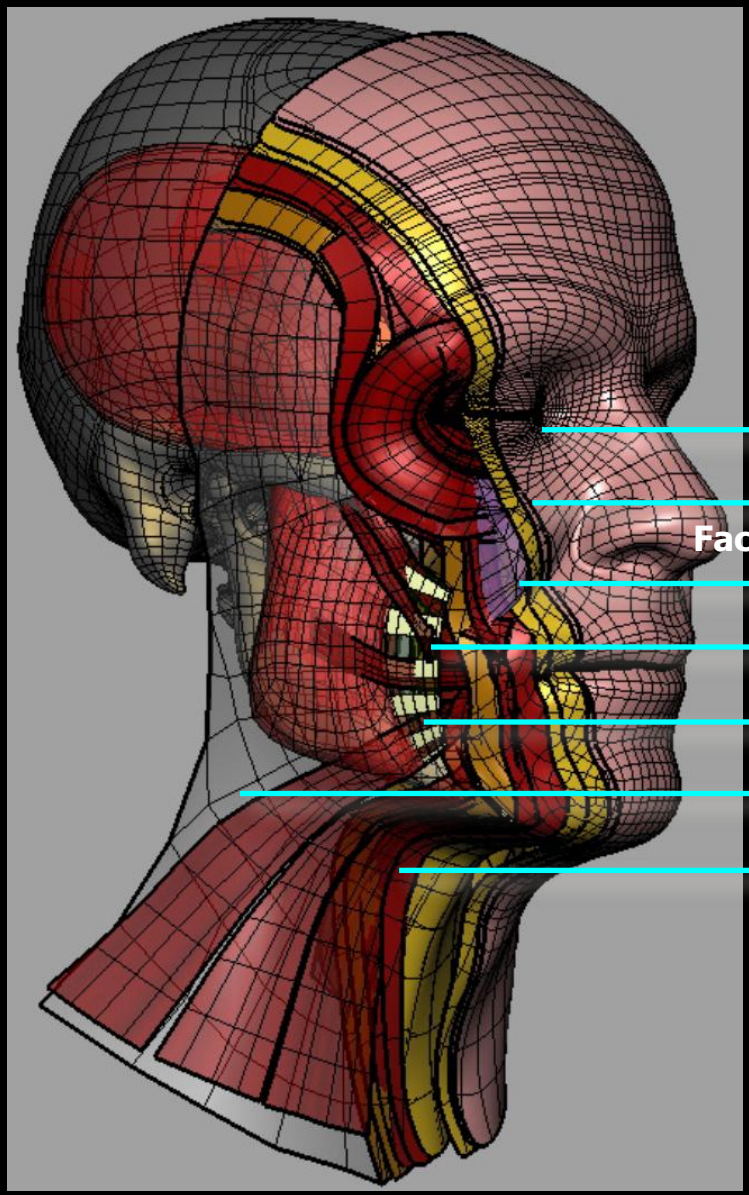


Faville et al. *BiophysJ*. 96, 4834-4852, 2009. Biophysically based mathematical modeling of interstitial cells of Cajal slow wave activity generated from a discrete unitary potential basis.

1. Circulatory system
2. Respiratory system
3. Musculo-skeletal system
4. Digestive system
5. **Brain & facial muscles**

Lab for Animate Technologies
Mark Sagar
David Bullivant

Modelling the facial muscles



Skin / Dermis

Hypodermis

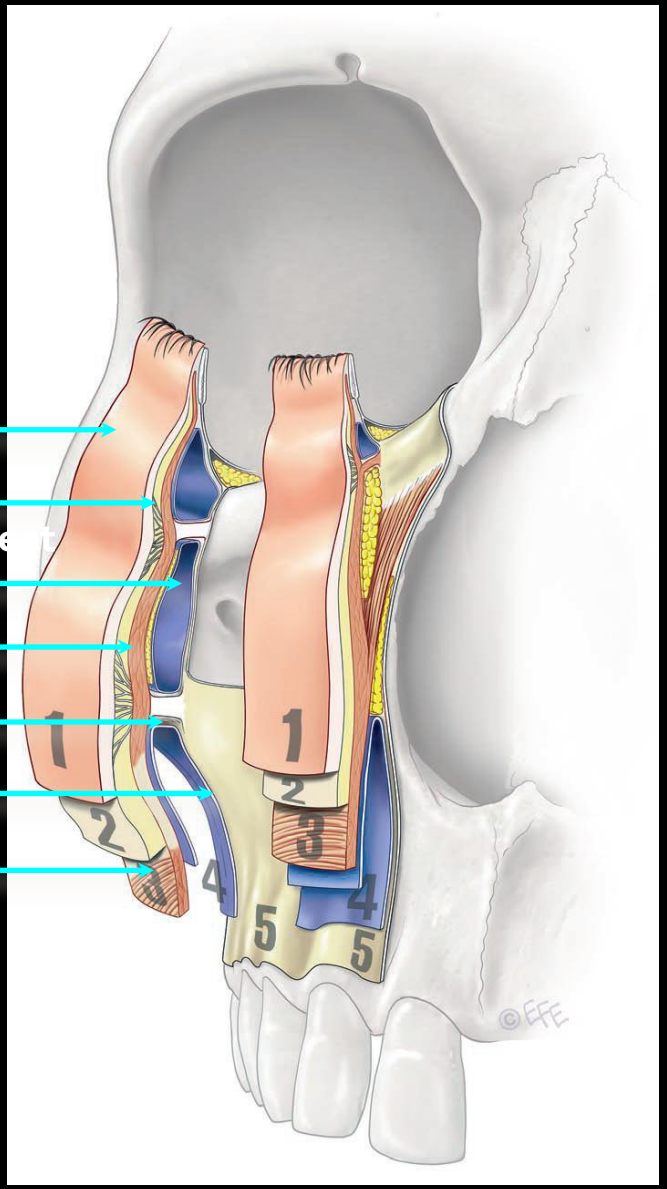
Facial Space / Fat Compartment

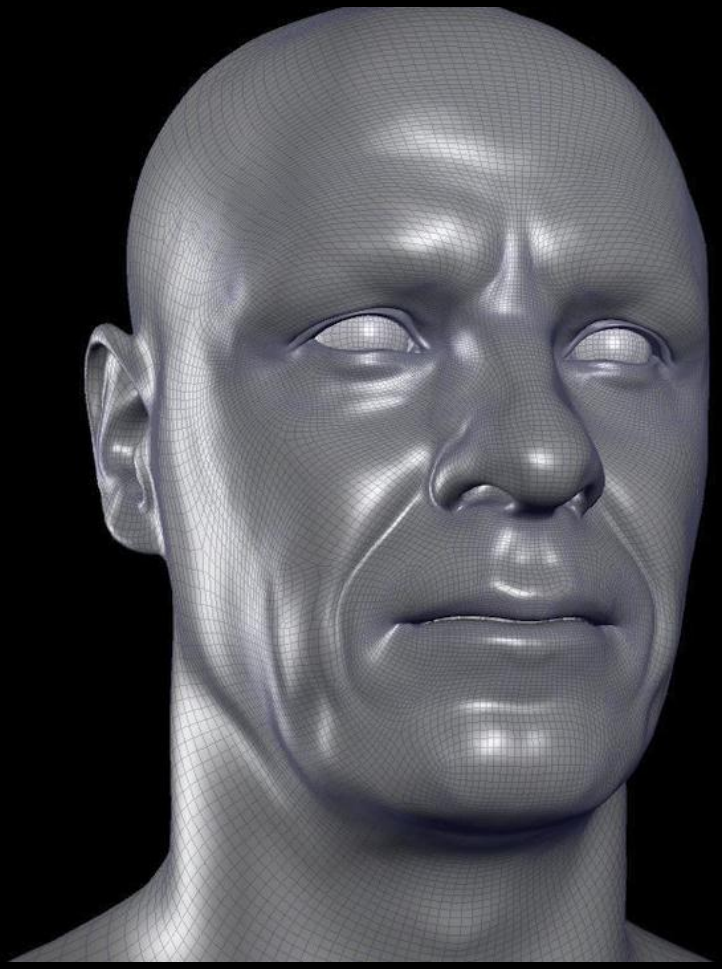
Muscle Fibres

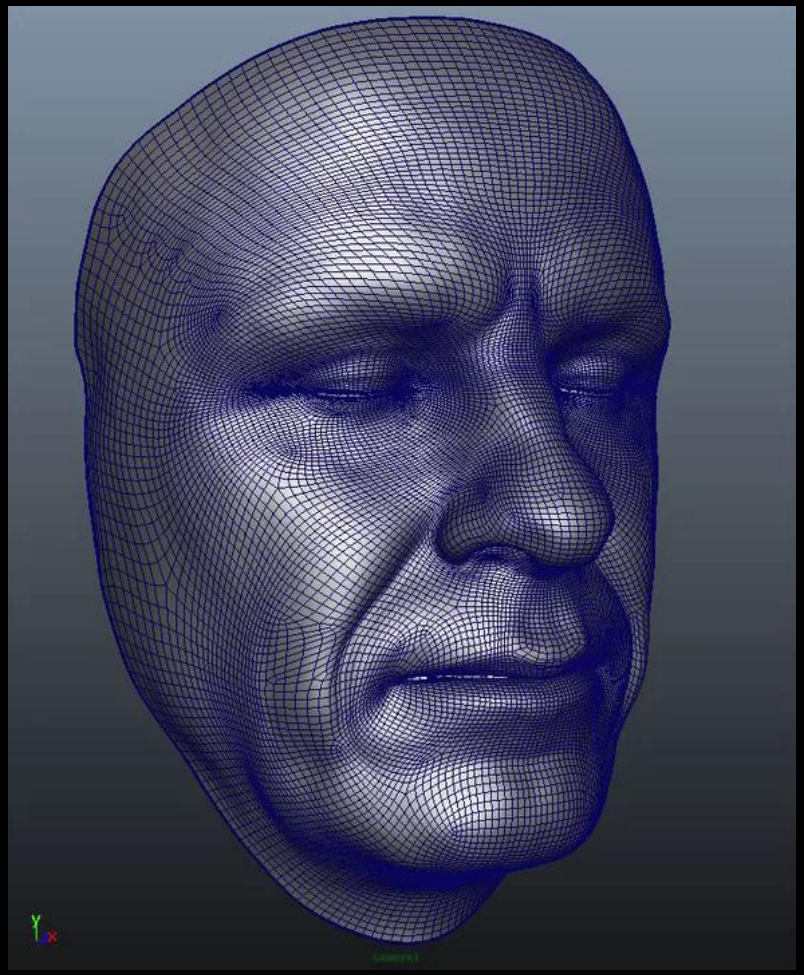
Ligament

Deep Fascia

SMAS

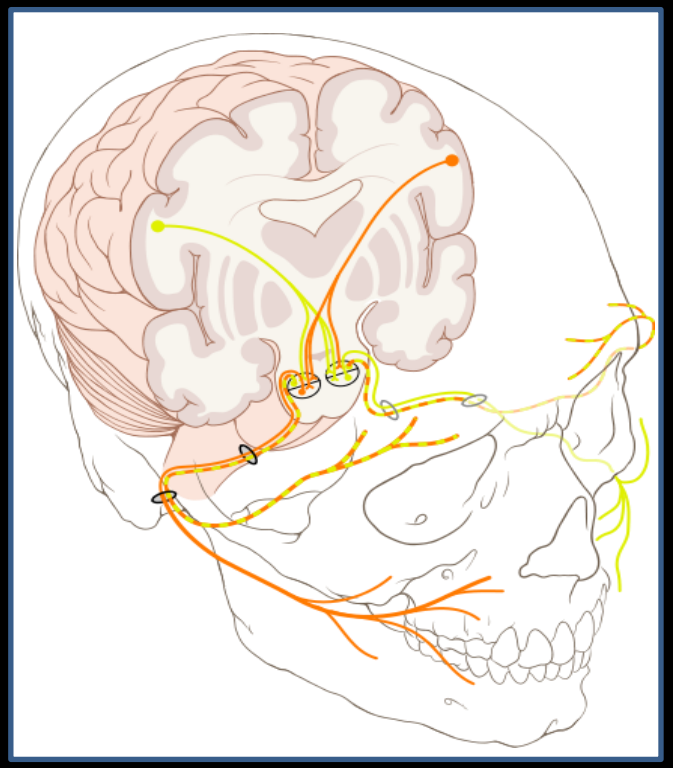






Muscles need a control system

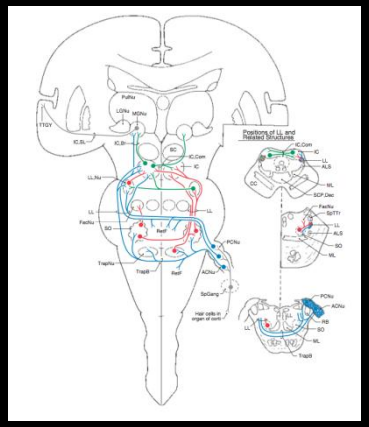
Facial Nerve Circuits

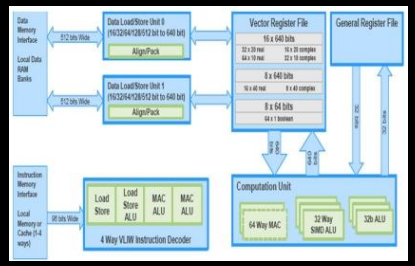


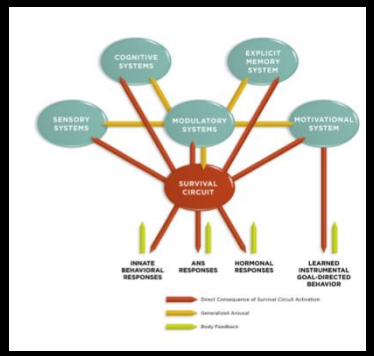
Models include

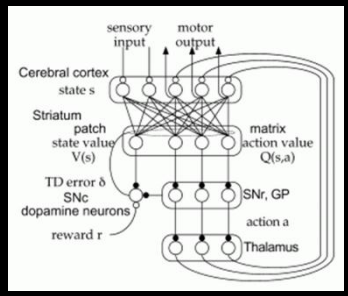
- **Neurobehavioral Models**
- **Emotion and Motivation**
- **Learning**
- **Neuronal Dynamics**

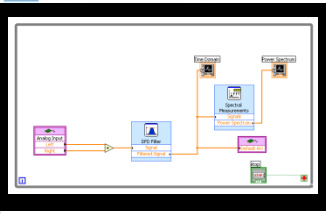
Multi-scale neural modeling

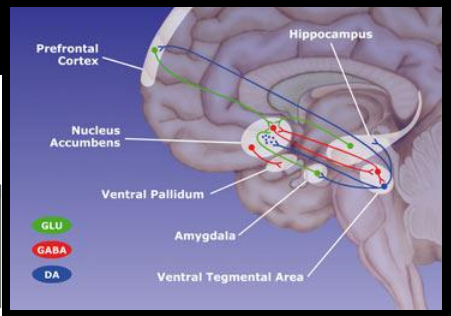


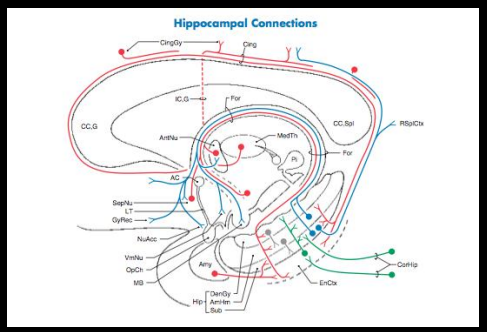


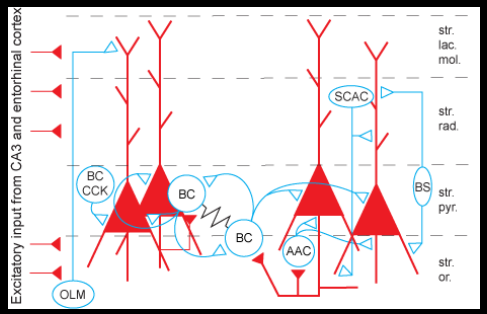


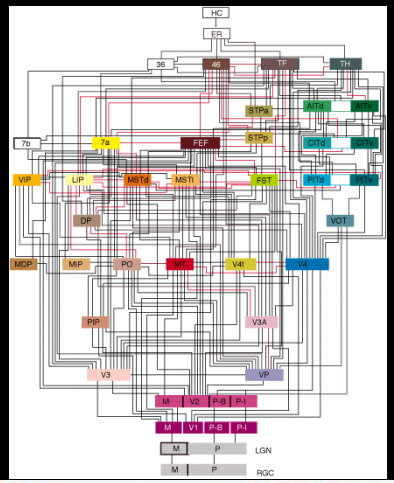


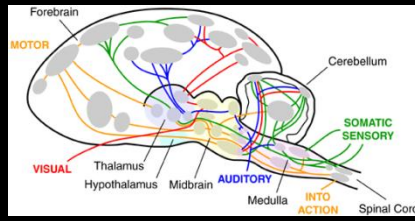


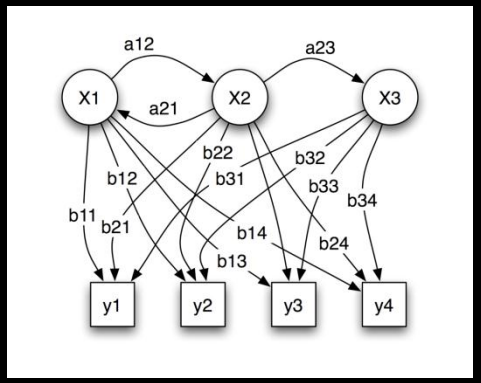


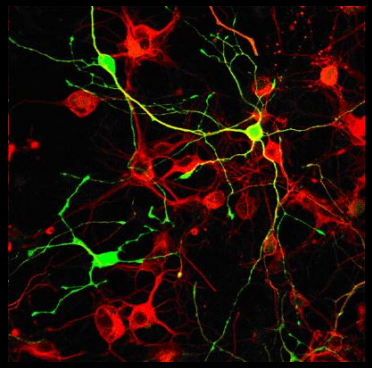


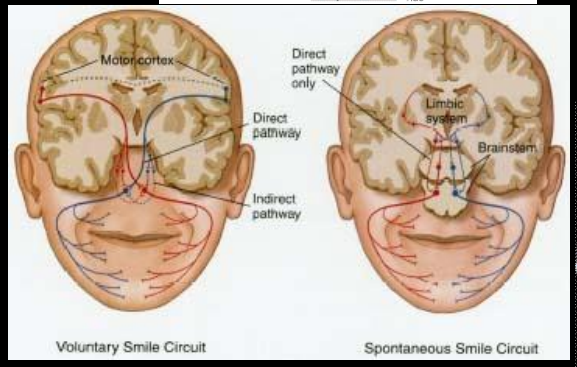


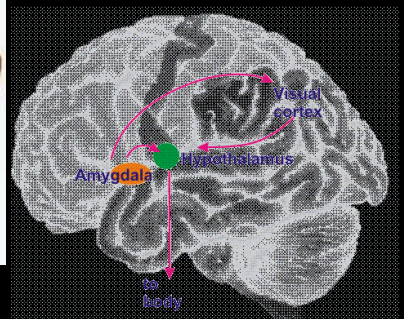












Part 2

To cope with the multi-physics, multi-scale, complexity of human biology we must create reproducible models with modular approaches based upon data and modelling standards

History of Physiome Project

1997 IUPS Physiome Committee

1998 CellML, FieldML

1999 Systems Biology Markup Language

2003 IMAG (NIH, NSF, FDA, NASA, DOE, DOD, ..)

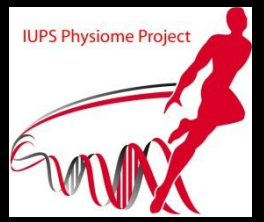
2006 STEP: Strategy for European Physiome

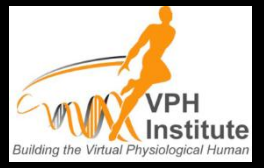
2008 VPH Network of Excellence

2009 Drug Disease Model Resources (DDMoRe)

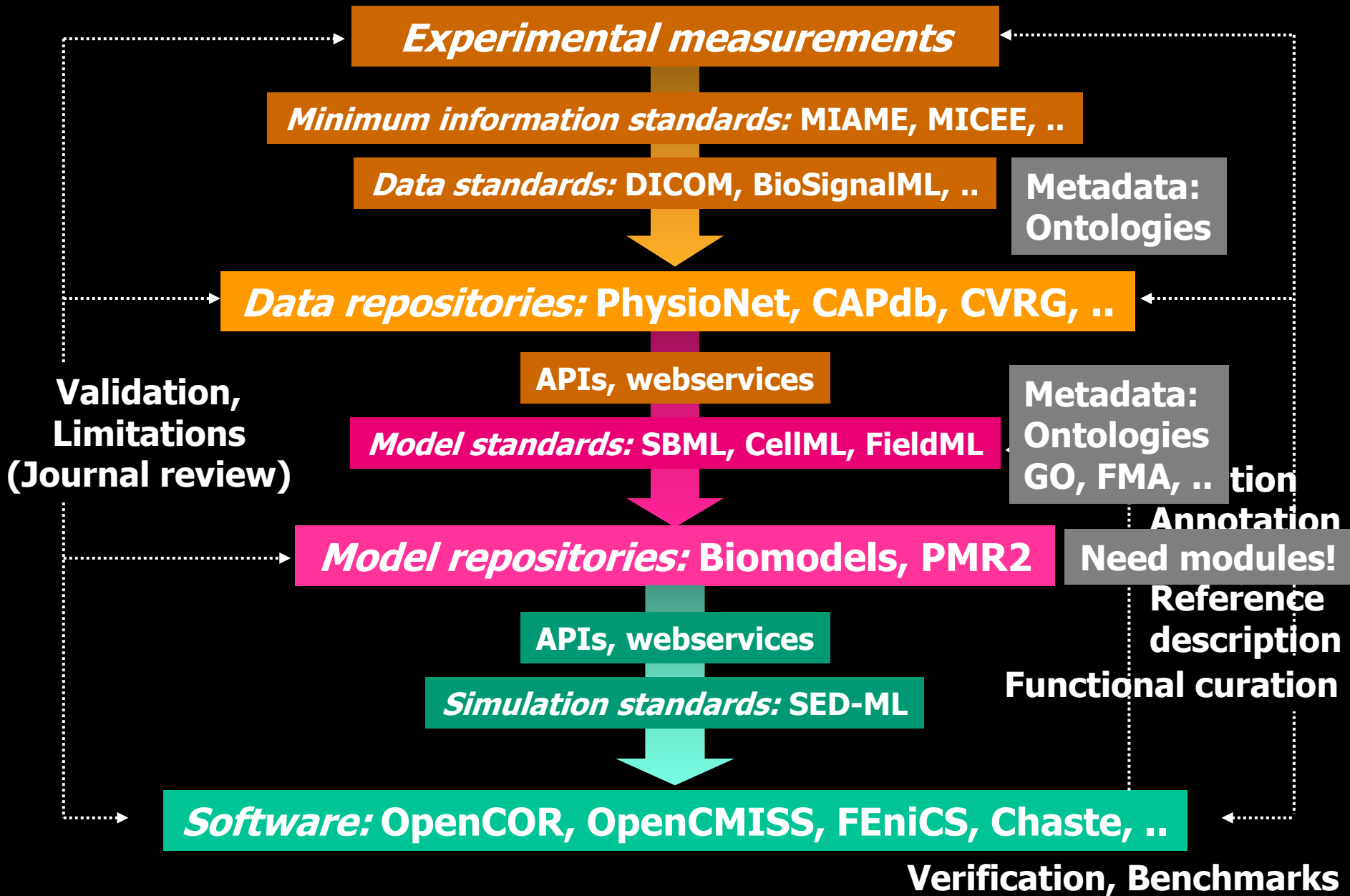
2010 German Virtual Liver Network

2011 VPH Institute





Standards for models, data & software



Note on model publishing

Biophysical Journal

"To assure public access to computational models, authors are strongly encouraged to deposit their models in the CellML Model Repository models.cellml.org/cellml or Biomodels Database www.ebi.ac.uk/biomodels-main/"

Similarly for many other journals.

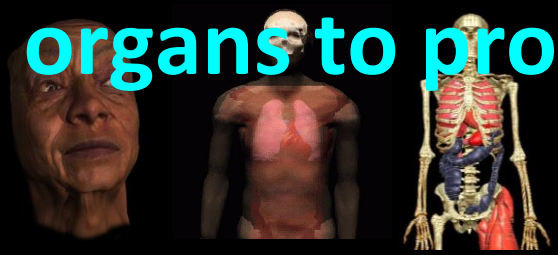
The challenge: organs to proteins

Environment

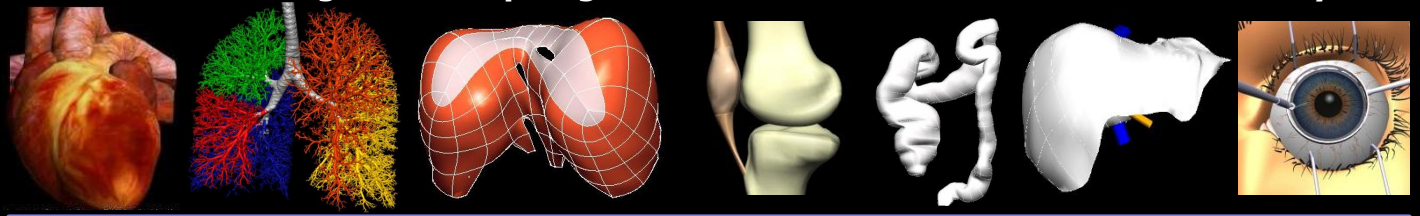
Organism

Organ system

Organ



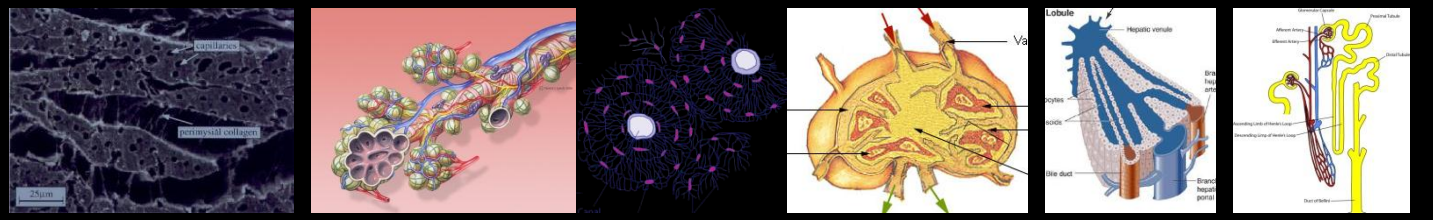
Heart | Lungs | Diaphragm | Knee | Colon | Liver | Eye



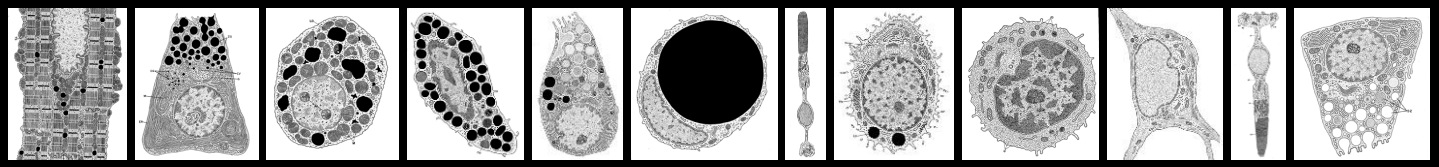
↑ x 1million ↓ 20 generations

Tissue

Cardiac sheets | Acinus | Osteon | Lymph node | Liver lobule | Nephron



Cell

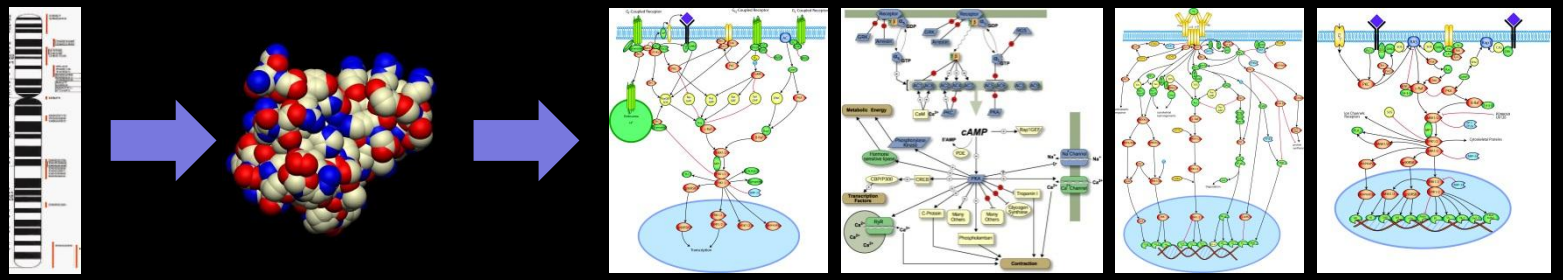


Network

Protein

Gene

Atom

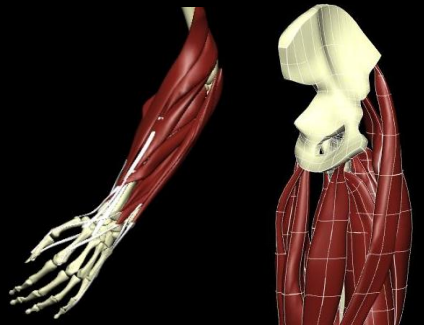


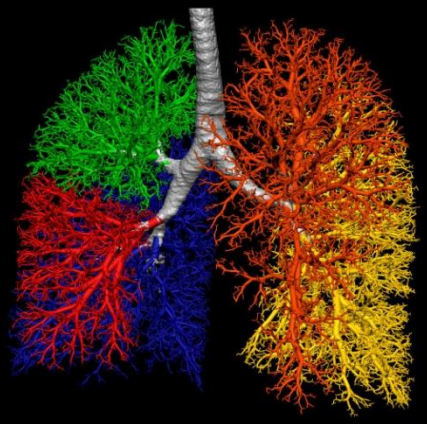
A multi-scale bioengineering approach needs:

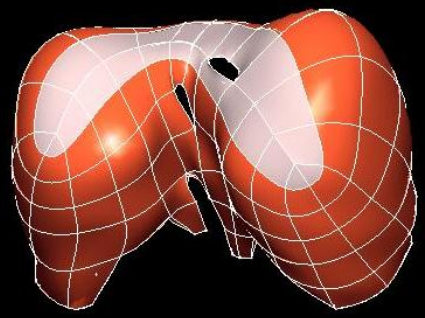
- Biophysically based models at every level
  – as much as possible (there's always a black box!)
- Adoption of model and data standards
  – SBML, CellML, FieldML for models
- Automated assembly of multi-scale models
  – molecule to organ(ism)
- Automated model reduction
  – otherwise too expensive
- New instrumentation
  – new instruments → new expts → new knowledge

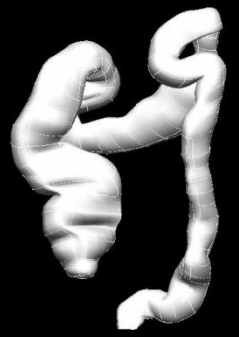
Organ system Physiome Projects

Cardiovascular system
Respiratory system
Musculo-skeletal system
Digestive system
Skin (integument)
Urinary system
Lymphoid system
Female reproductive system
Special sense organs
Central nervous system
Endocrine system
Male reproductive system





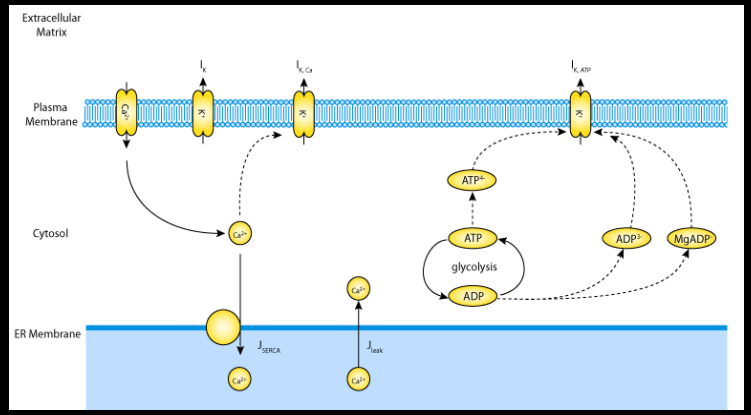




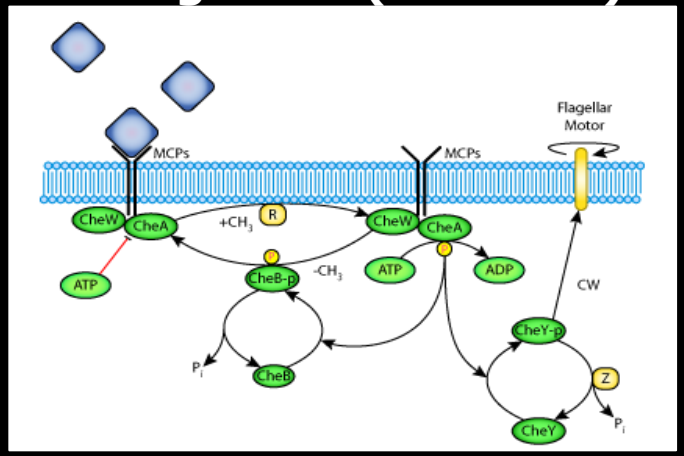
CellML – standards, databases and tools

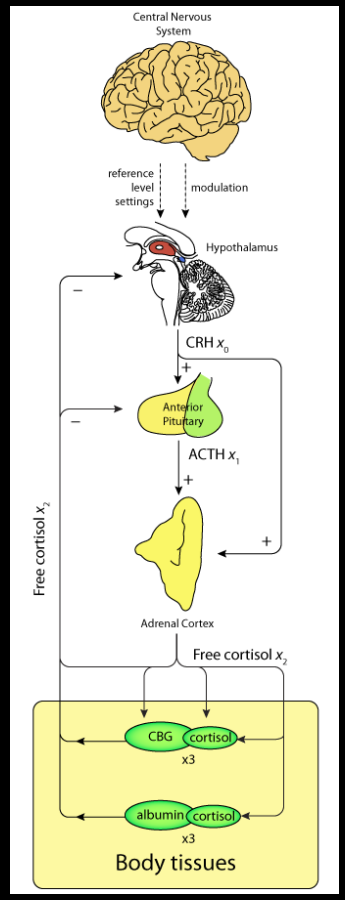
Cuellar AA, Lloyd CM, Nielsen PF, Halstead MDB, Bullivant DP, Nickerson DP, Hunter PJ. An overview of CellML 1.1, a biological model description language. *SIMULATION: Transactions of the Society for Modeling and Simulation*, 79(12):740-747, 2003

Calcium dynamics (63 models)

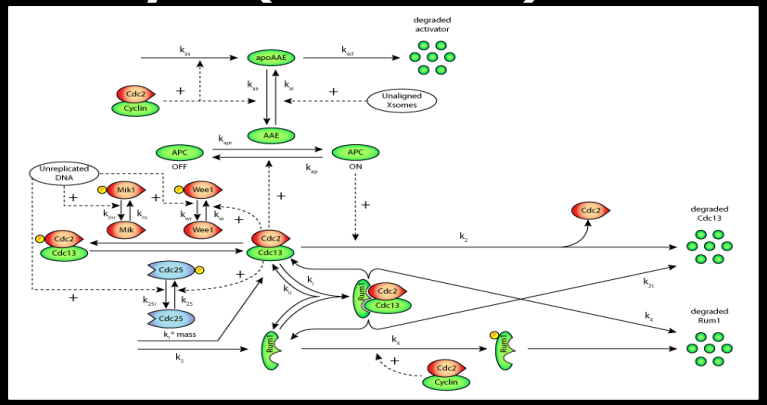


Cell migration (2 models)

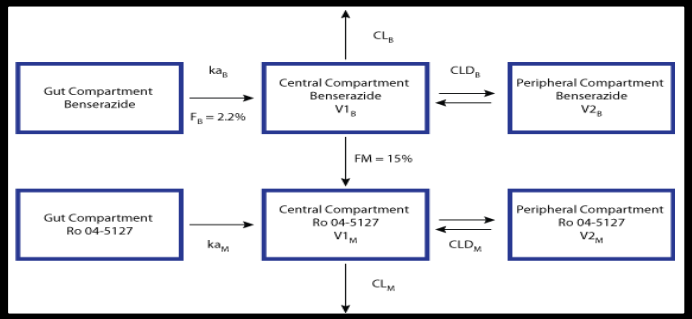




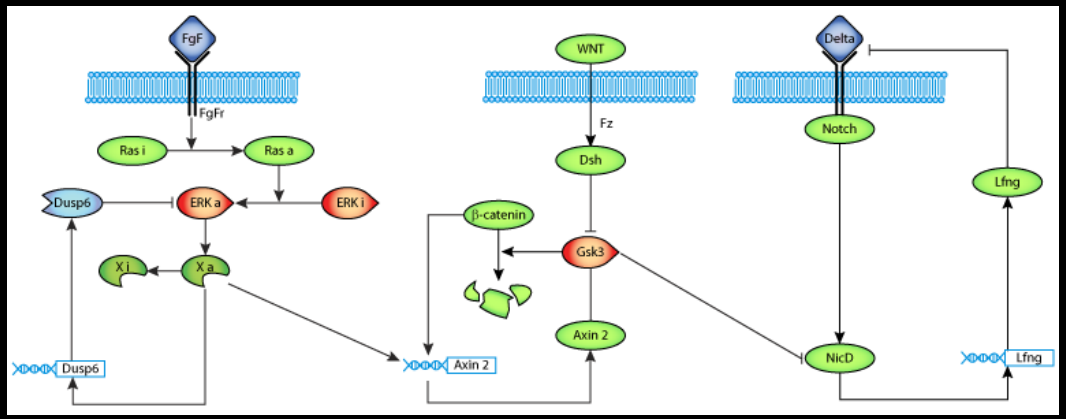
Cell cycle (25 models)



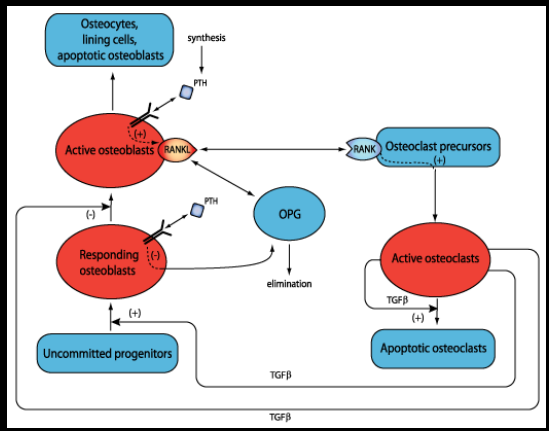
PKPD models (7 models)



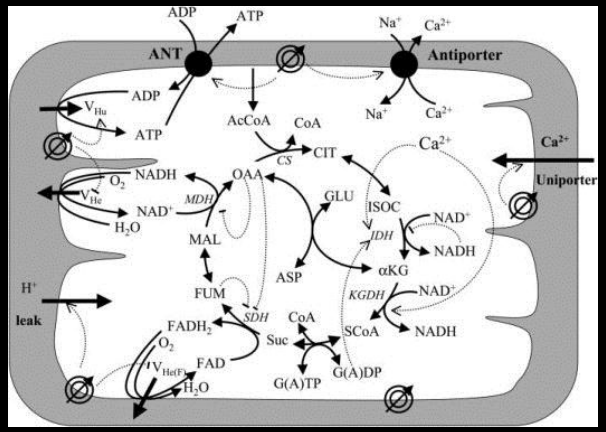
Circadian rhythms (9 models)



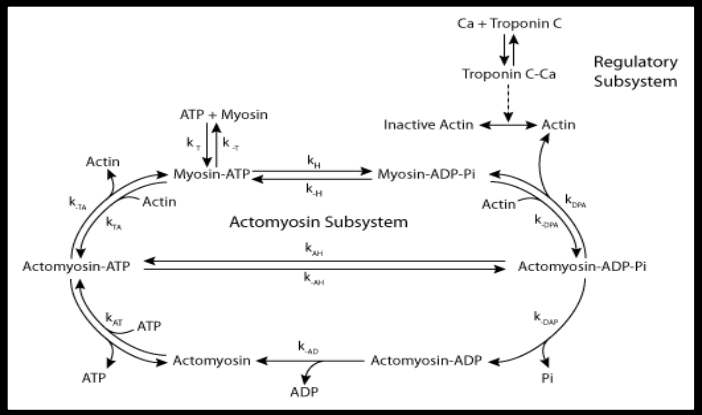
Endocrine system (29)



Metabolism (35 models)

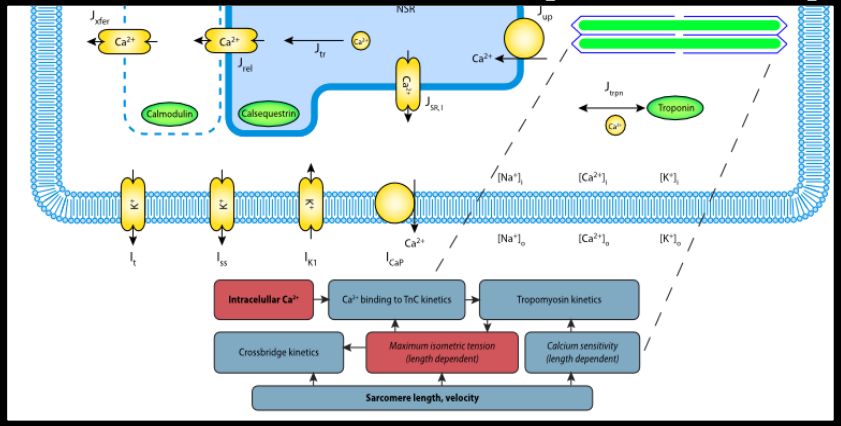


Myofilament mechanics (15)

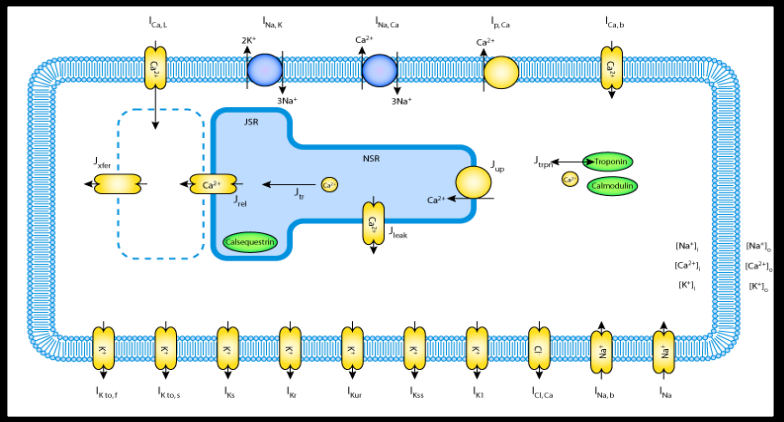


Material constitutive laws

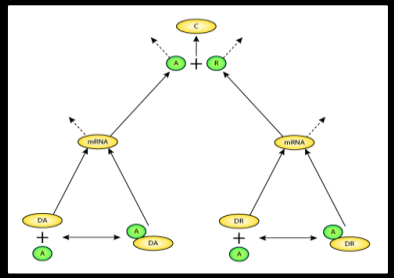
Excitation-contaction (15 models)

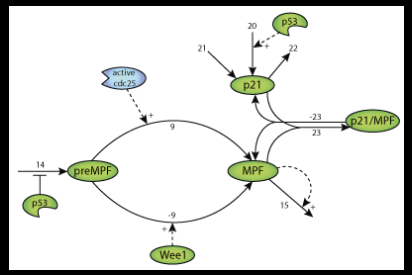


Electrophysiology (117 models)

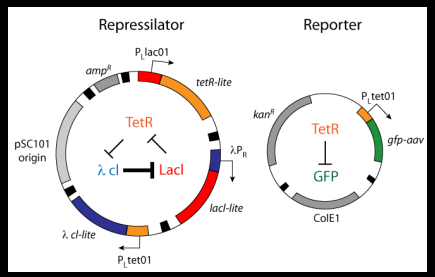


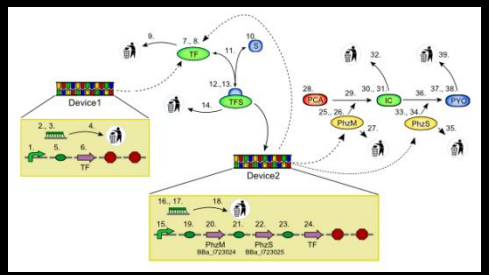
Gene regulation DNA repair (3)



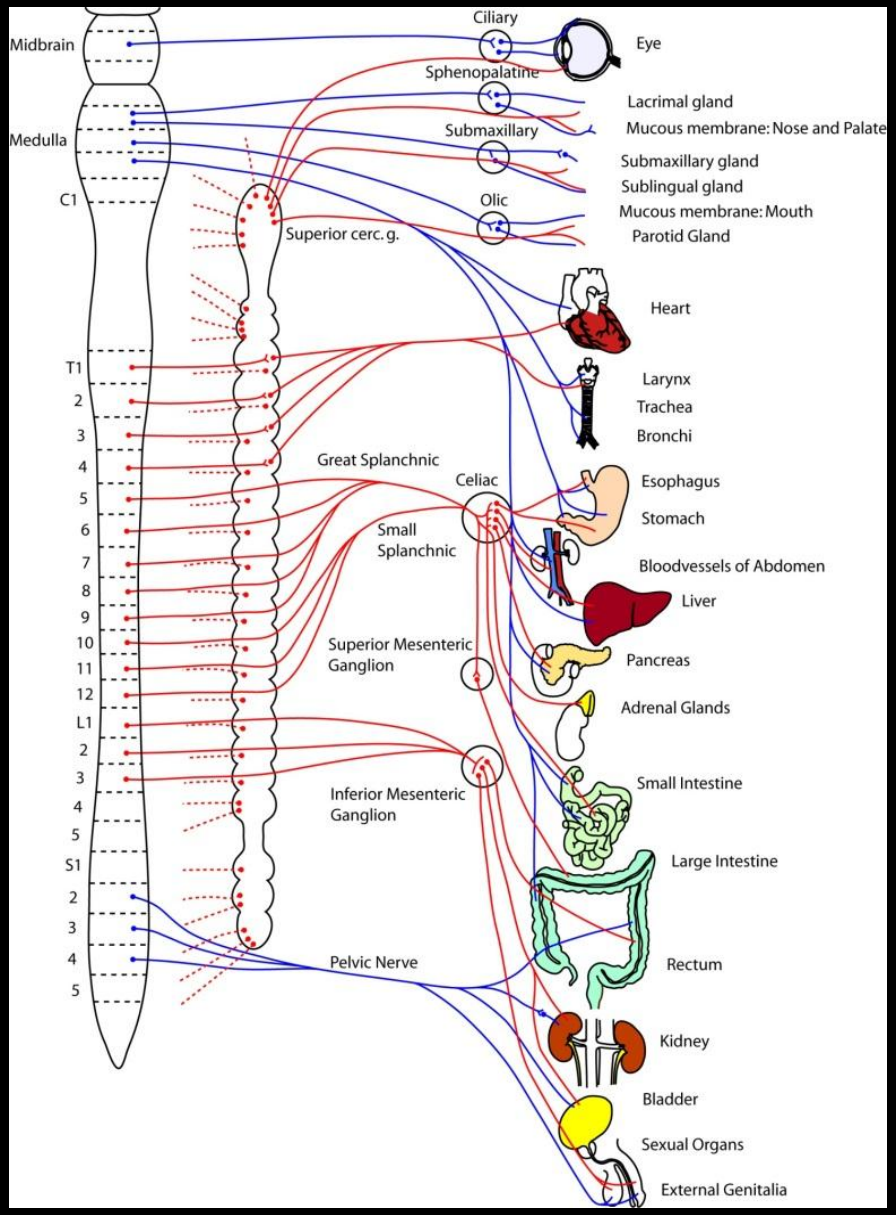


Synthetic biology (5 models)

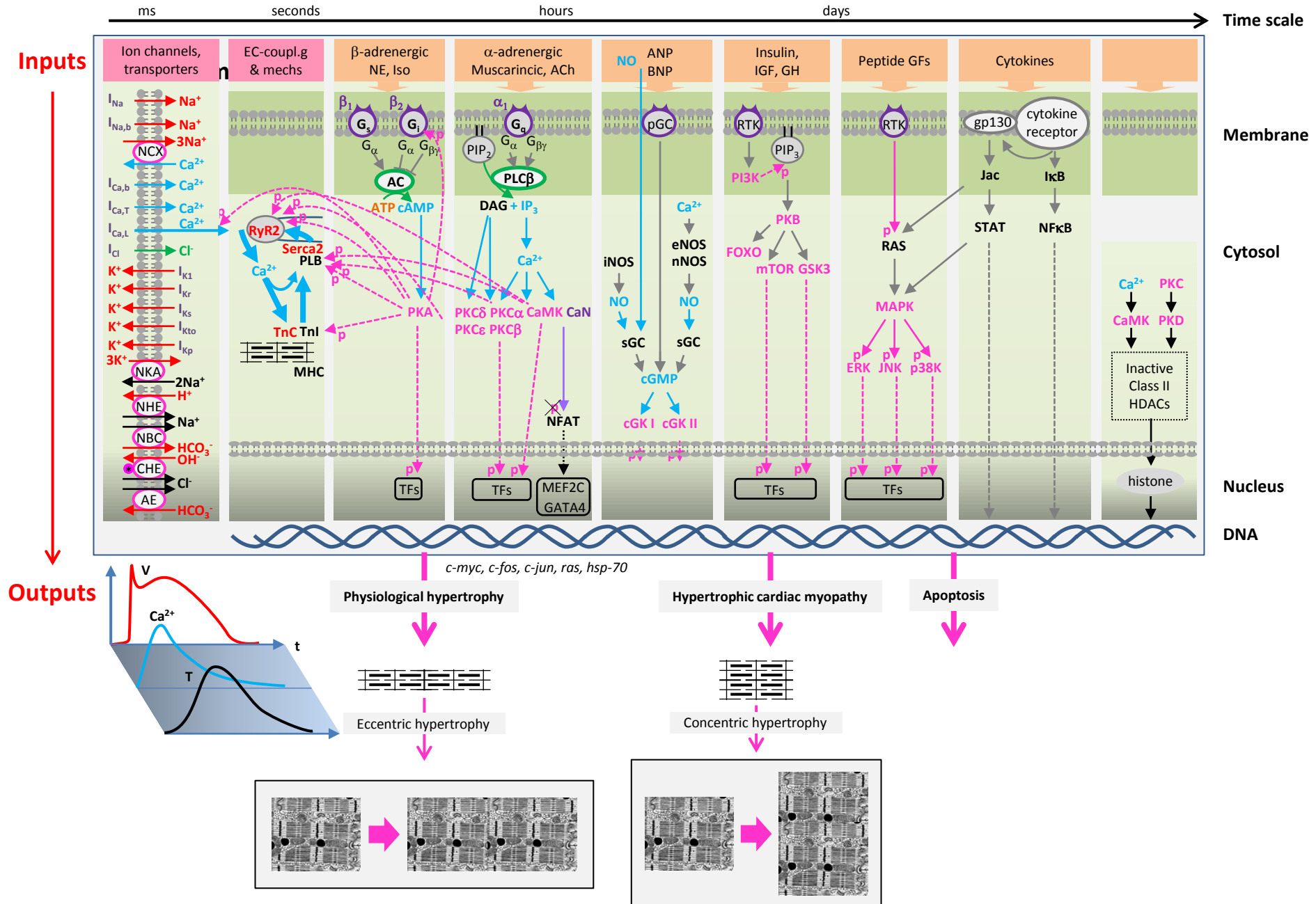




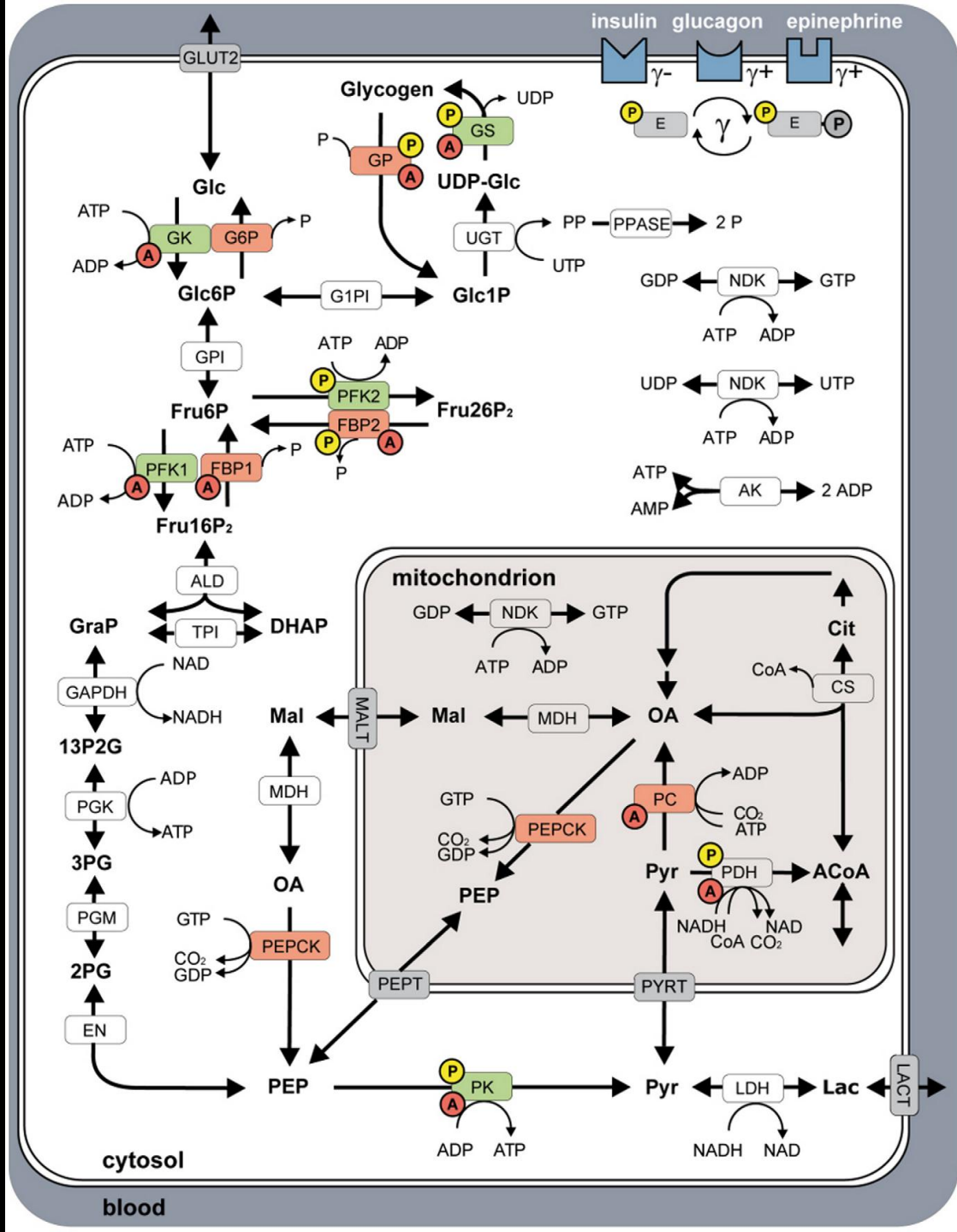
CellML enables modular construction



CellML signalling modules for the cardiac myocyte

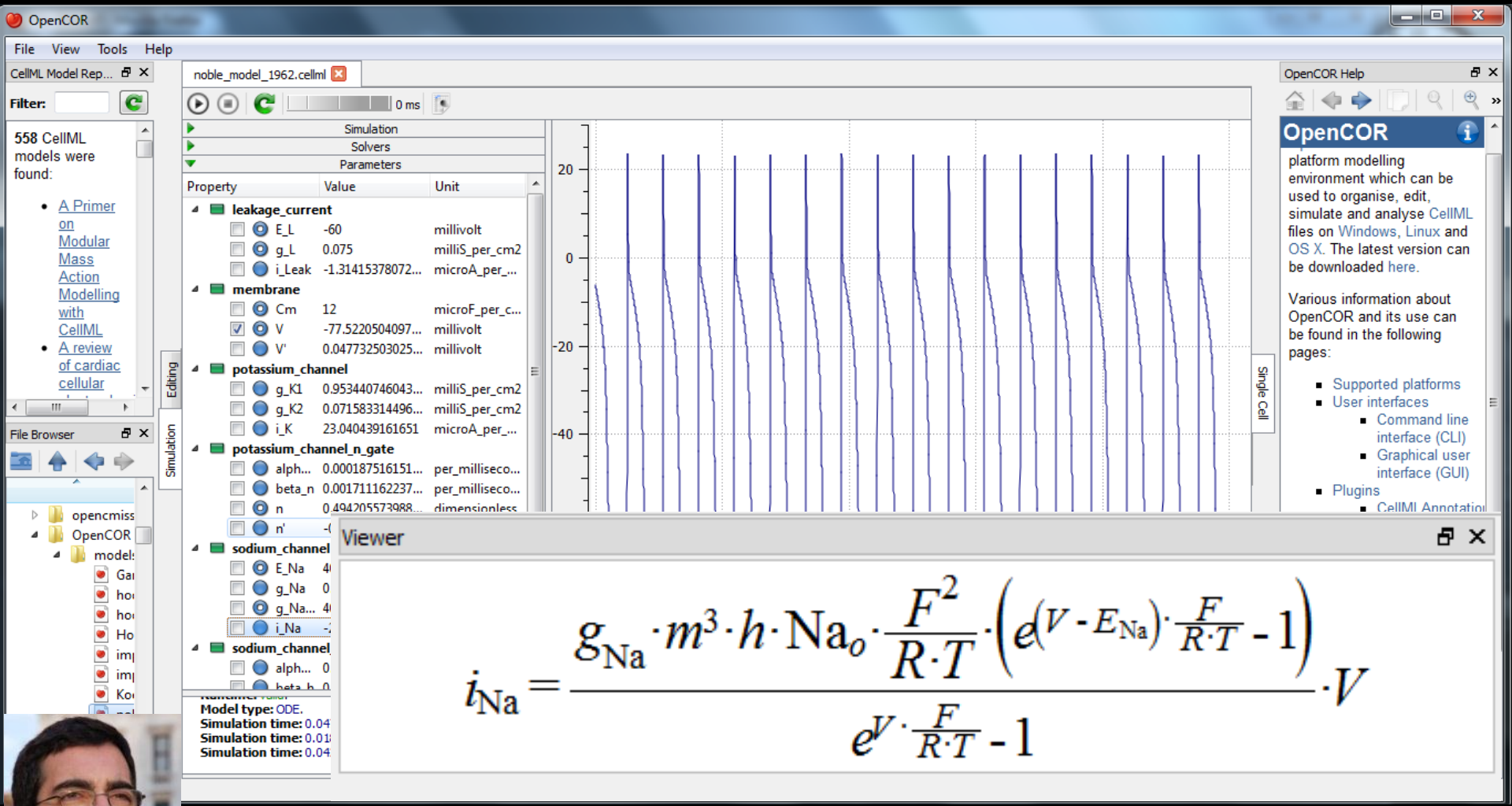


- Glucose transporter (GLUT2)
- Glucokinase (GK)
- Glucose-6 phosphatase (G6Pase)
- Glucose-6-phosphate isomerase (GPI)
- Glucose-1-phosphate 1,6-phosphomutase (G16PI)
- UTP: Glucose-1-phosphate uridylyltransferase (UGT)
- Pyrophosphate phosphohydrolase (PPase)
- Glycogen synthase (GS)
- Glycogen phosphorylase (GP)
- Nucleosid diphosphate kinase (NDK)
- Adenylate kinase (AK)
- Phosphofructo kinase 2 (PFK2)
- Fructo-2,6-bisphosphatase (FBP2)
- Phosphofructo kinase (PFK1)
- Fructose-1,6-bisphosphatase (FBP1)
- Aldolase (ALD)
- Triosephosphate isomerase (TPI)
- D-Glyceraldehyde-3-phosphate: NAD+ oxidoreductase (GAPDH)
- Phosphoglycerate kinase (PGK)
- 3-Phosphoglycerate mutase (PGM)
- Enolase (EN)
- Pyruvate kinase (PK)
- Phosphoenolpyruvate carboxykinase (PEPCK)
- Pyruvate carboxylase (PC)
- Lactate dehydrogenase (LDH)
- Lactate transporter (LACT)
- Pyruvate transporter (PYRT)
- PEP transporter (PEPT)
- Pyruvate dehydrogenase (PDH)
- Citrate synthase (CS)
- Nucleosid diphosphate kinase (NDK)
- Oxalacetate flux (OAAflx)
- Acetyl-CoA flux (ACOAflx)
- Citrate flux (CITflx)



www.cellml.org/tools

→ OpenCOR www.opencor.ws



Alan Garny

Linking models to medical informatics

Biotechnology Journal

DOI 10.1002/biot.201100304

Biotechnol. J. 2012, 7, 958–972

Integrating knowledge representation and quantitative modelling in physiology

Bernard de Bono[1,2,3] *and Peter Hunter*[1,4]

Bernard de Bono

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http://www.jbiomedsem.com/content/4/1/22

JOURNAL OF BIOMEDICAL SEMANTICS

RESEARCH Open Access

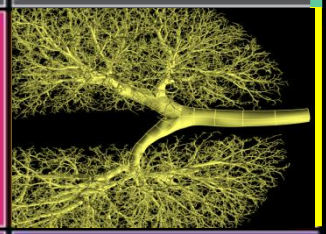
Functional tissue units and their primary tissue motifs in multi-scale physiology

Bernard de Bono[1,2*], Pierre Grenon[3], Richard Baldock[4] and Peter Hunter[1]

J Physiol 592.11 (2014) pp 2389–2401

Biophysical constraints on the evolution of tissue structure and function

P. J. Hunter[1,2] and B. de Bono[1,3]

Large Intestine	Jejuno-Ileum	Liver Pancreas Duodenum	Stomach	Esophagus	Mouth Throat
Genitals Gonads	Vascular Caudal	Vascular Abdominal	Vascular Cardiac	Vascular Cephalic	
Urinary Tract	Nervous Caudal	Nervous Lower Spinal	Nervous Upper Spinal	Nervous Cephalic	Nasopharynx Conjunctiva
Lower Limb	Pelvis	Abdomen	Thorax	Neck Upper Limb	Head

3D | Connections | Proteins | Search

Vascular Connection

vas:85064_0

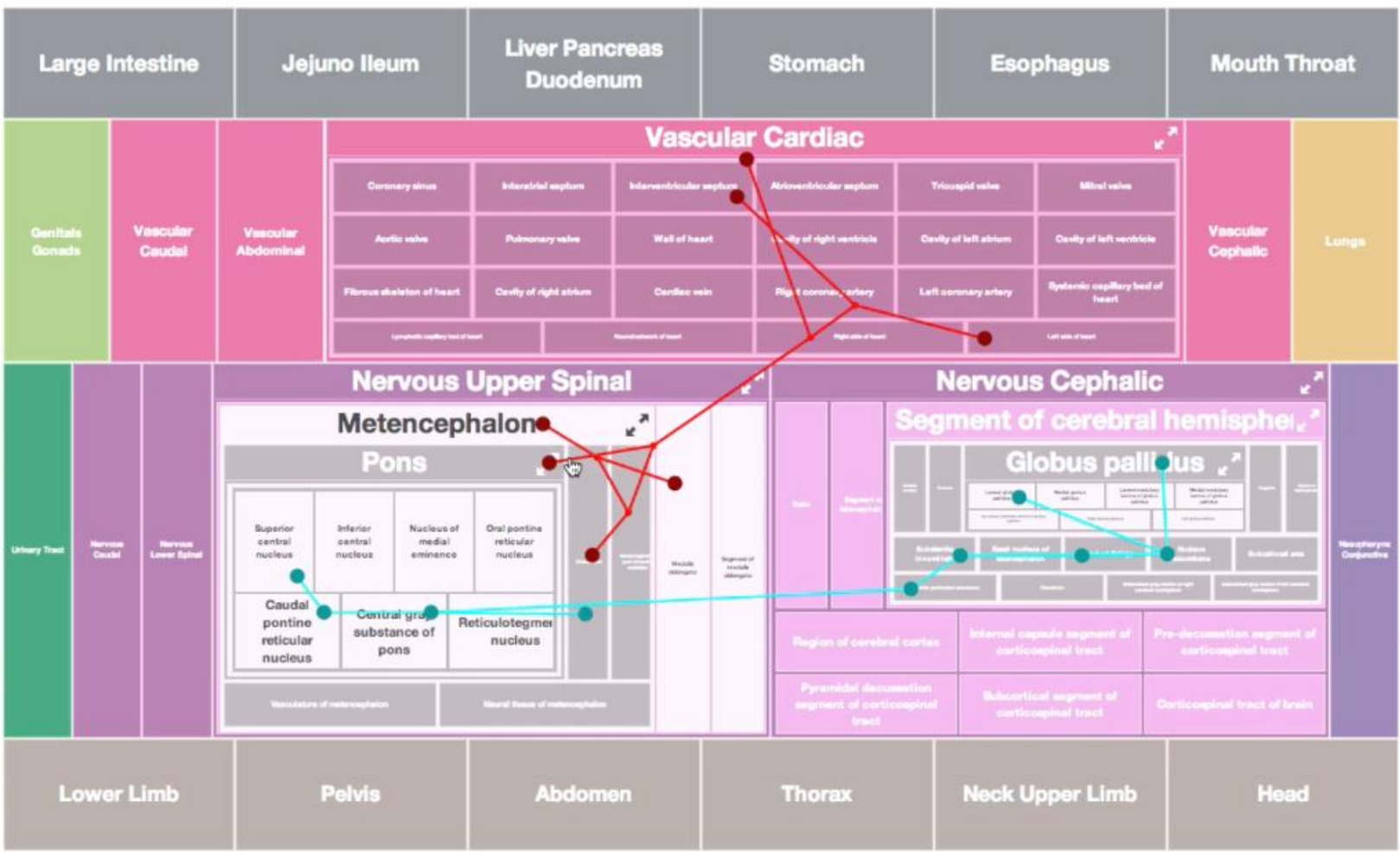
ID: 2772
Name: Arterial Segment 2772 of Trunk of right pontine artery from its origin to the origin of Trunk of medial branch of right pontine artery
At: Trunk of right pontine artery (fma:85064)

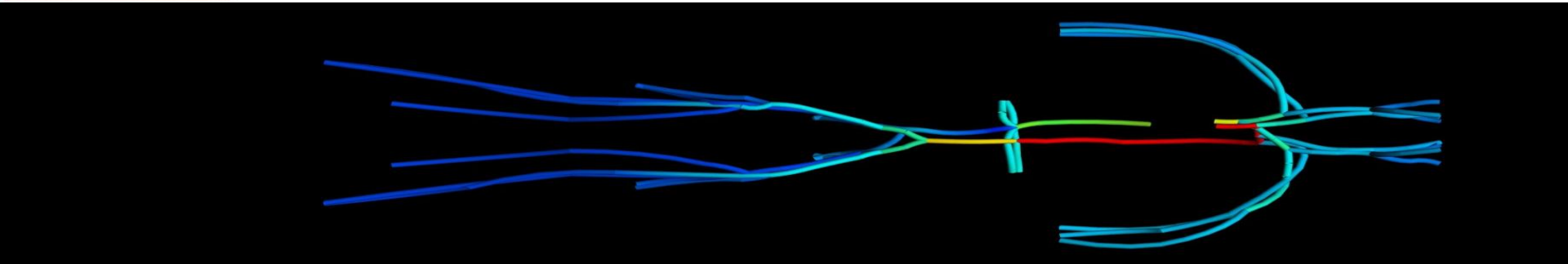
vas:50013001_0

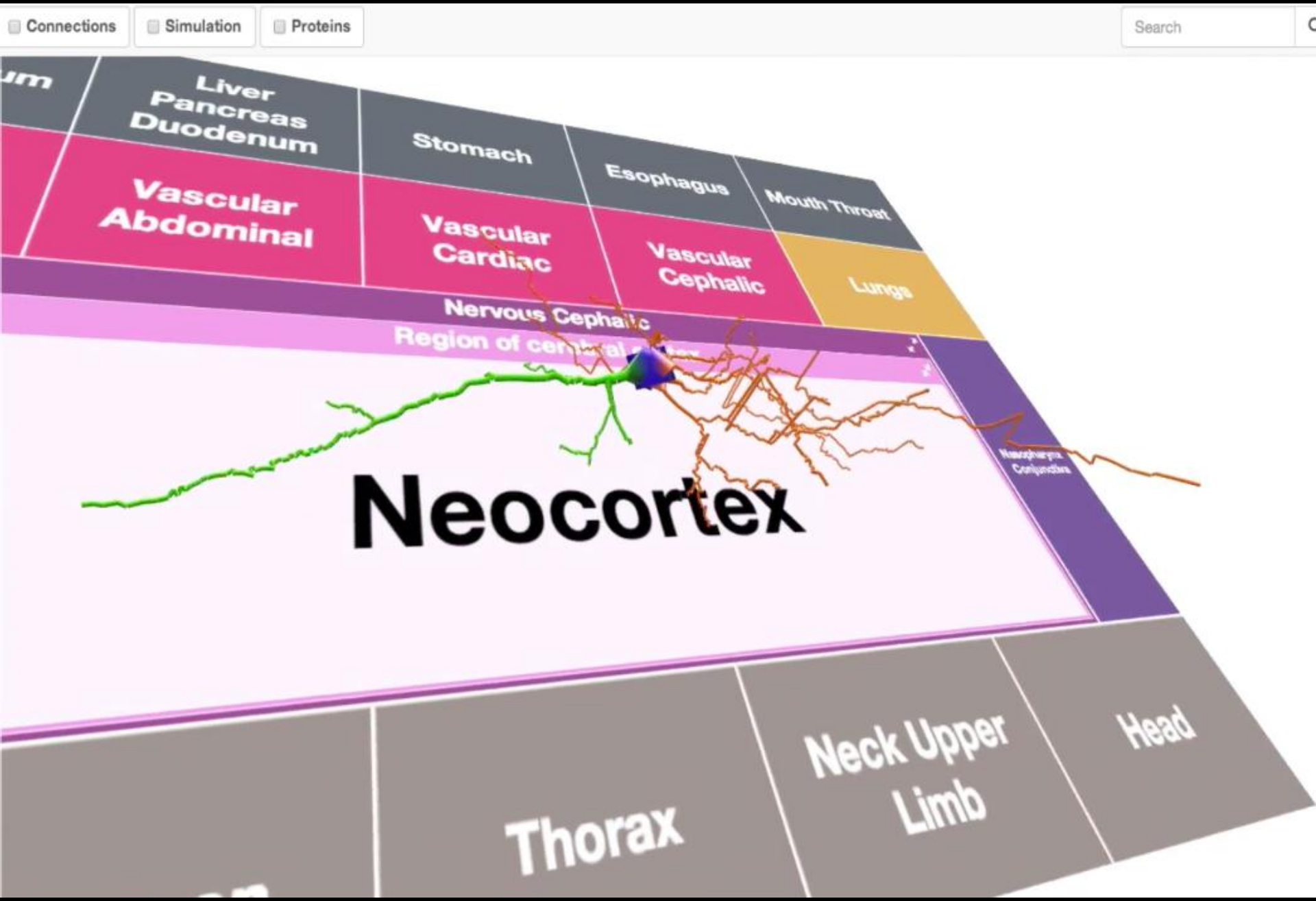
ID: 2774
Name: Arterial Segment 2774 of Trunk of right pontine artery from the origin of Trunk of medial branch of right pontine artery to the origin of Trunk of lateral branch of right pontine artery
At: Trunk of right pontine artery (fma:85064)

vas:50013466_0

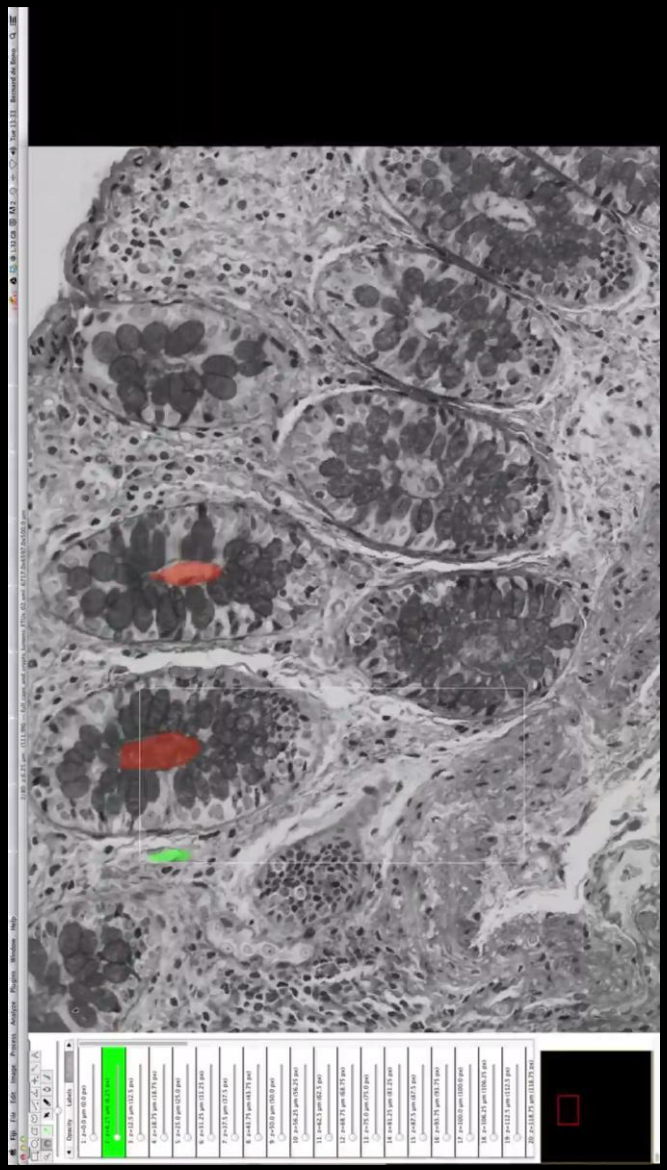
ID: 2776
Name: Arterial Segment 8888 of Trunk of right pontine artery from the origin of Trunk of lateral branch of right pontine artery to origin of terminal arteriolar segment to Metencephalon microcirculation
At: Trunk of right pontine artery (fma:85064)



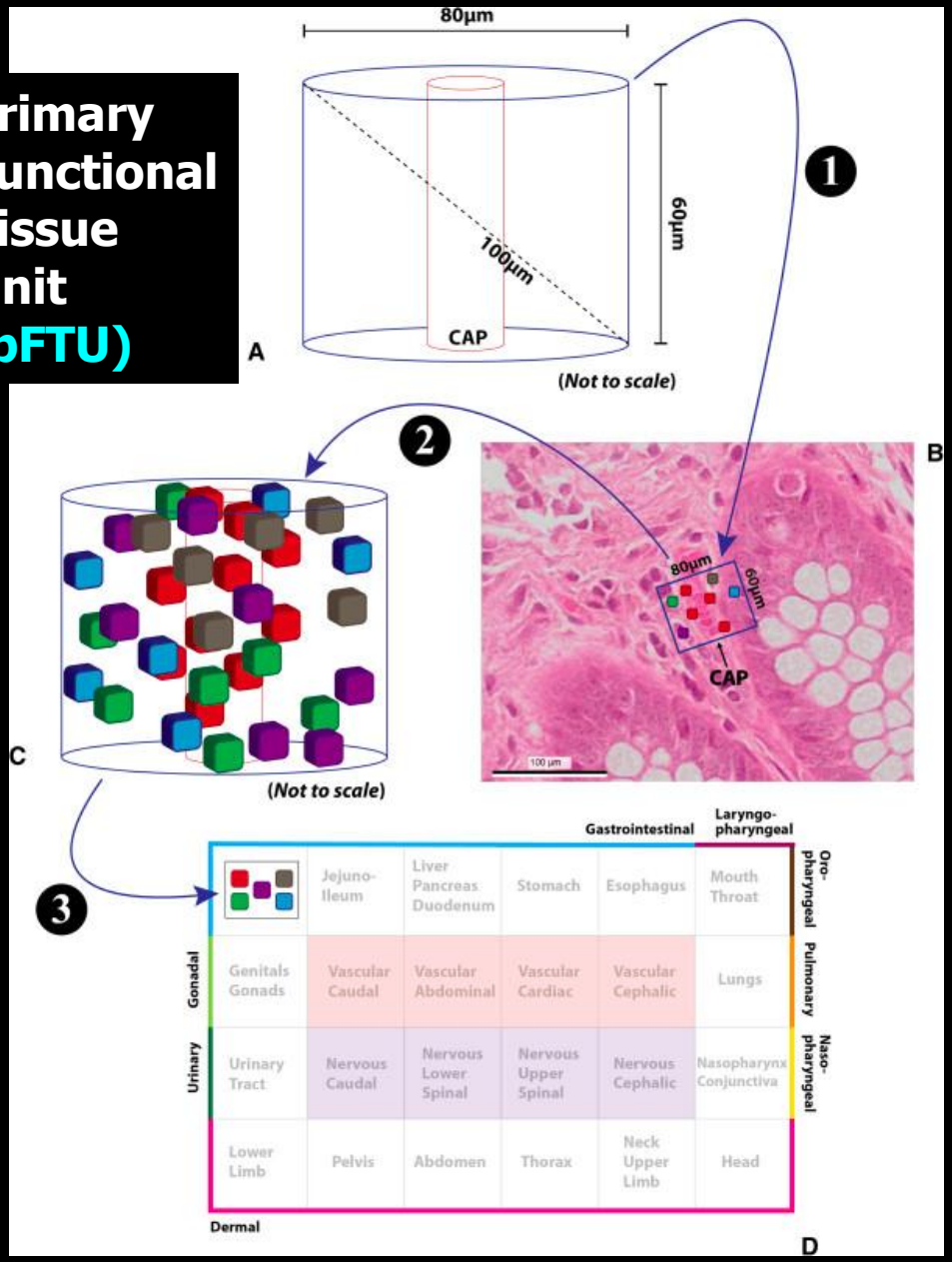



Connections
Simulation
Proteins
Search
Liver
Pancreas
Duodenum
Stomach
Esophagus
Mouth Throat
Vascular
Abdominal
Vascular
Cardiac
Vascular
Cephalic
Lungs
Nervous Cephalic
Neocortex
Thorax
Neck Upper
Limb
Head

Functional tissue units



primary Functional Tissue Unit (pFTU)

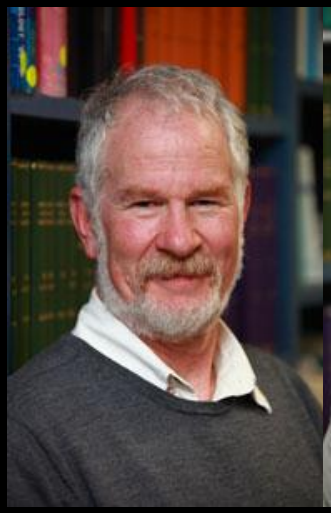


Organ	Tissue	Cells	Cell function
URINARY SYSTEM (all pFTUs include B, EC, SMC, FB, PC, MP)			
Kidney	Nephron (Bowman's capsule Glomerulus Proximal tubule Loop of Henle Distal tubule Collecting duct)	mesangial cell podocyte	specialized SMC wrap around capillaries of glomerulus
		juxtaglomerular cell proximal tubule cell thin segment epithelial cell principal cell of collecting duct intercalated cell	s. renin (specialised SMC) Na^+ & H_2O uptake; H^+/ HCO_3^- exchange; s. organic acids descending limb of Henle highly permeable to H_2O ascending limb of Henle impermeable to H_2O control Na^+ & H_2O uptake in response to aldosterone and vasopressin acid-base homeostasis
Urinary bladder	Epithelial conduit	epithelial cell	barrier
Ureter	Epithelial conduit	epithelial cell	barrier
Urethra	Epithelial conduit	epithelial cell	barrier
ENDOCRINE SYSTEM (all pFTUs include B, EC, SMC, FB, PC, MP)			
Pituitary gland	Adeno-hypophysis	somatotrope (GH cell) lactotrope (PRL cell) corticoptrope (ACTH cell) gonadotrope (FSH & LH cells) thyrotrope (TSH cell)	s. growth hormone (GH) s. prolactin (PRL) (s. milk production, gonadal function) s. ACTH (s. cortisol secretion from adrenal cortex) s. FSH & LH (control gonadal function) s. TSH (s. release of thyroxin from thyroid gland)
	Neuro-hypophysis		
Thyroid gland	Thyroid gland	follicular epithelial cell parafollicular cell	s. thyroid hormones (thyroxine & triiodothyronine) s. calcitonin
Parathyroid glands	Parathyroid gland	principal cell oxyphil cell	s. parathyroid hormone s. parathyroid hormone-related protein (PTHrP) & calcitriol
Adrenal gland	Adrenal medulla	chromaffin cell	s. catecholamines (neuroendocrine cells)
	Adrenal cortex	adrenocortical cells	s. aldosterone and cortisol
Endocrine pancreas	Islet of Langerhan	α cell β cell δ cell	s. glucagon s. insulin s. somatostatin
Pineal gland	Pineal gland	pinealocyte	s. melatonin
IMMUNE SYSTEM (all pFTUs include B, EC, SMC, FB, PC, MP)			
Bone marrow		haemopoietic cell mesenchymal cell osteoprogenitor cell	pluripotent cell that generates blood cells multipotent stromal cell (SMC) → osteoblast, chondrocyte, adipocyte mesenchymal cell that differentiates into an osteoblast

Acknowledgements

ABI colleagues

Bruce Smaill



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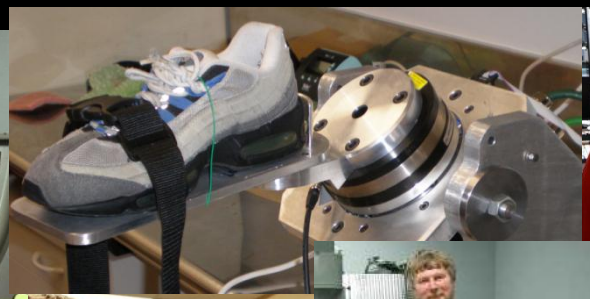
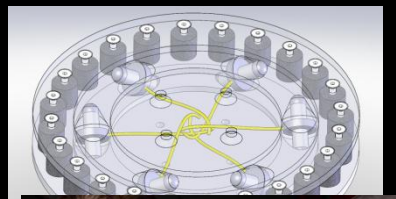
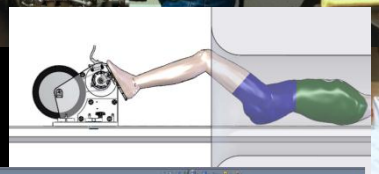
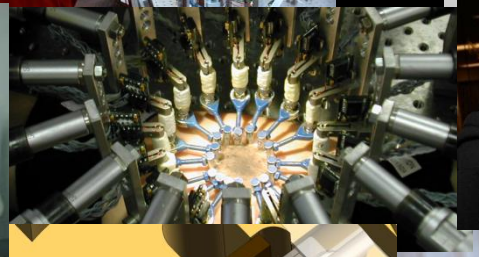
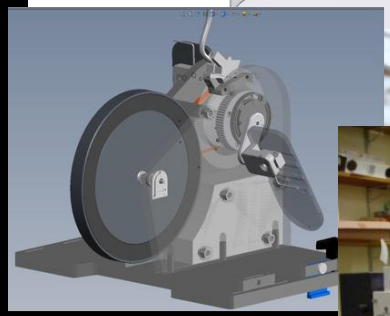
Our instrumentation engineers

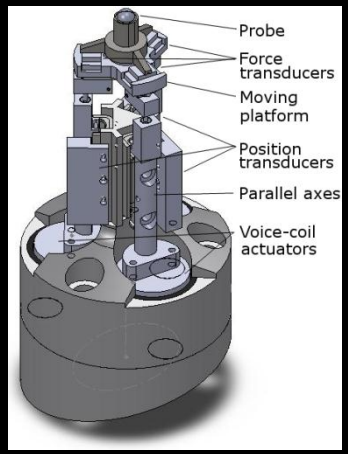



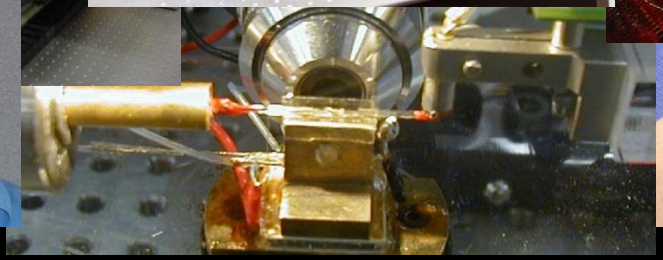









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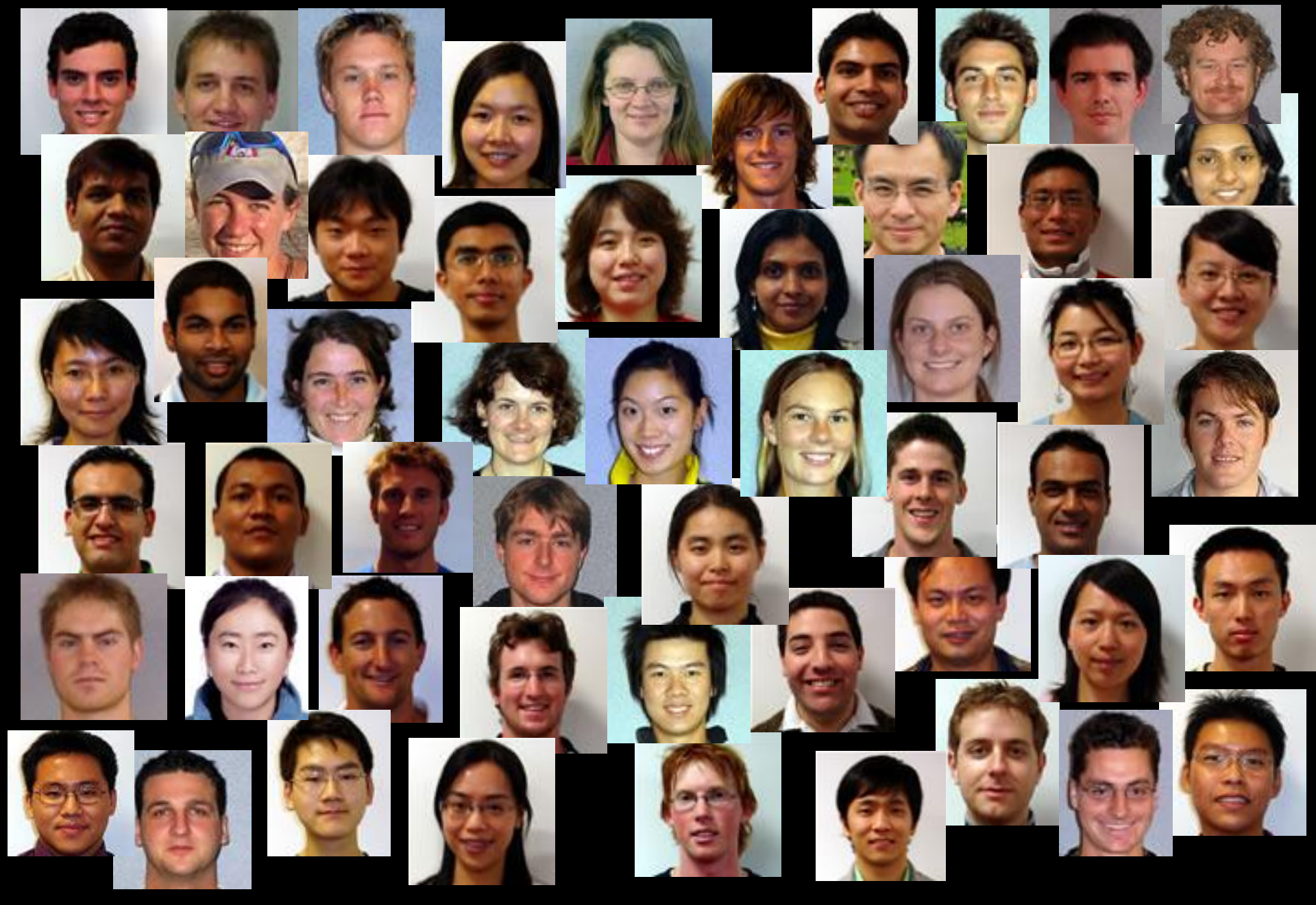

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