

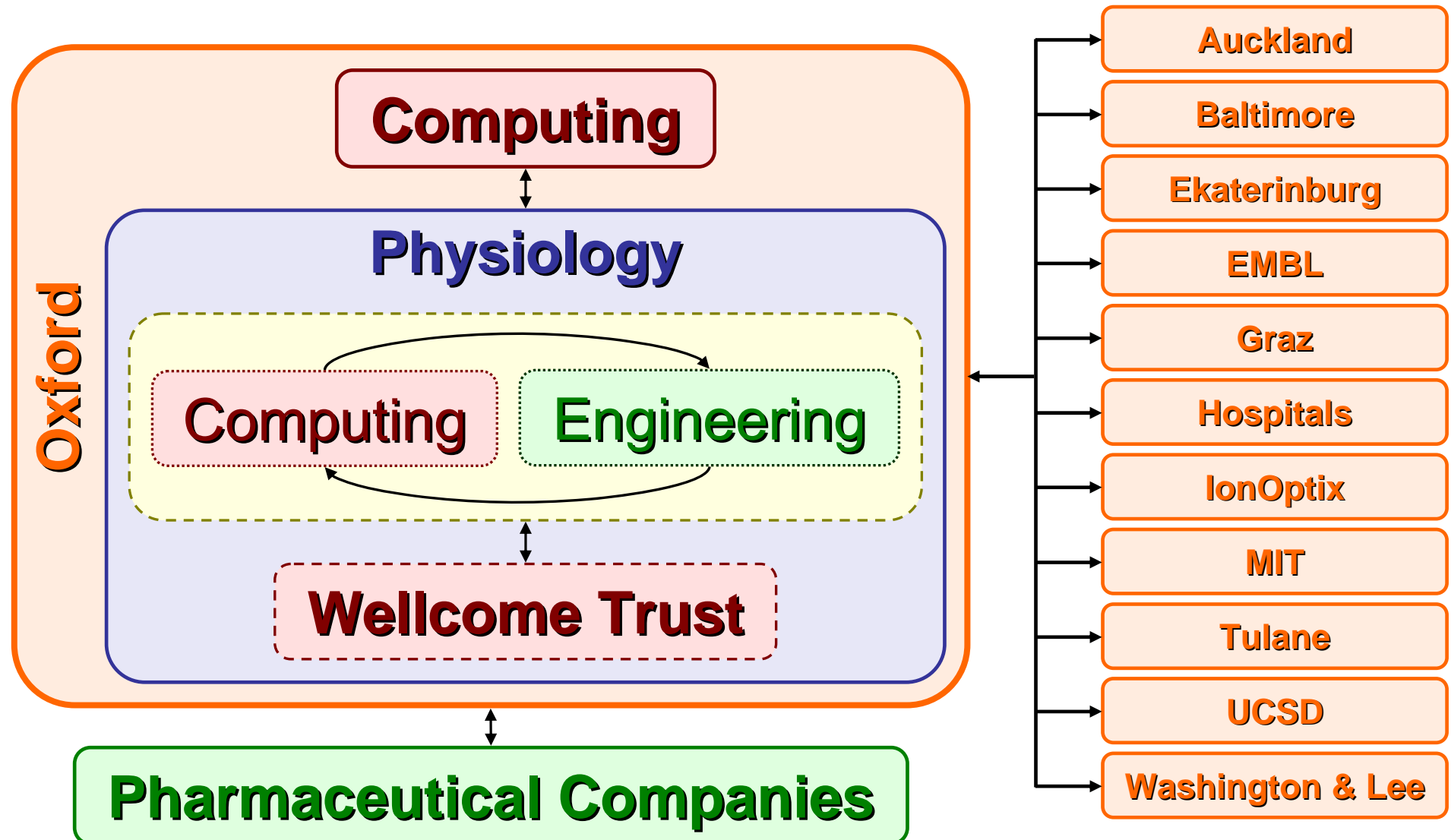
# Cardiac Research at the Interface of Computing and Engineering

*Alan Garny & Peter Kohl*



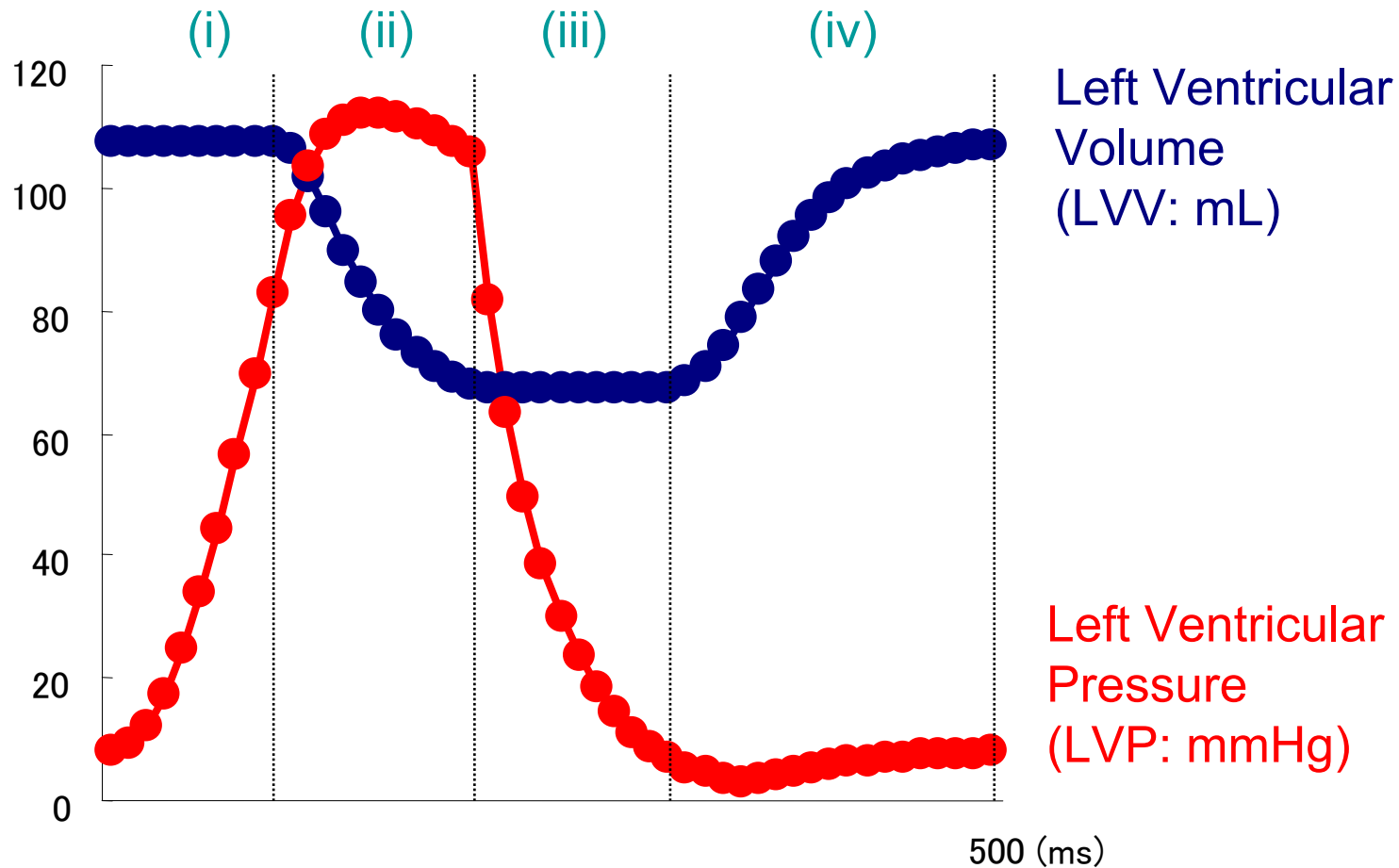
***European Cardiac Simulation Groups Meeting***  
*11-12 November 2005*

# Interactions at Oxford



# Physiology – Engineering

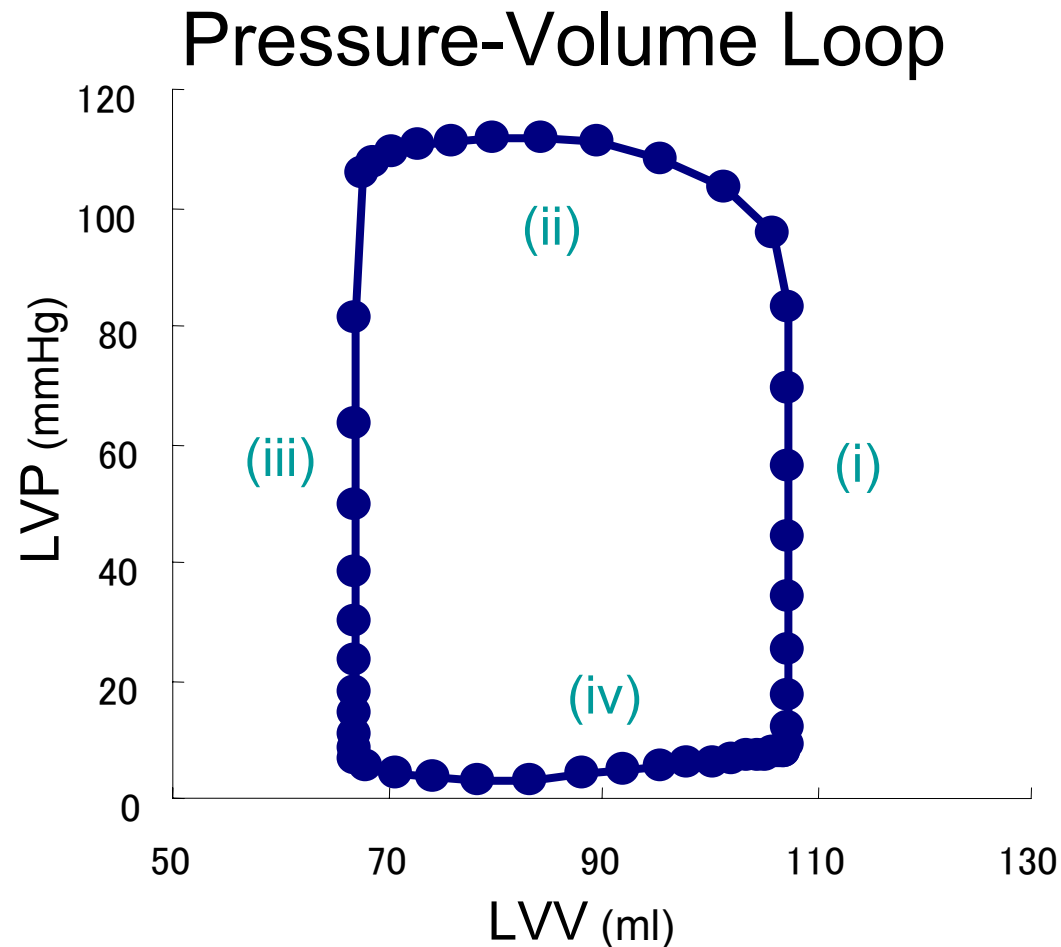
- **Cellular level: pressure-volume loop**



*Gentaro Iribe & Michiel Helmes (IonOptix)*

# Physiology – Engineering

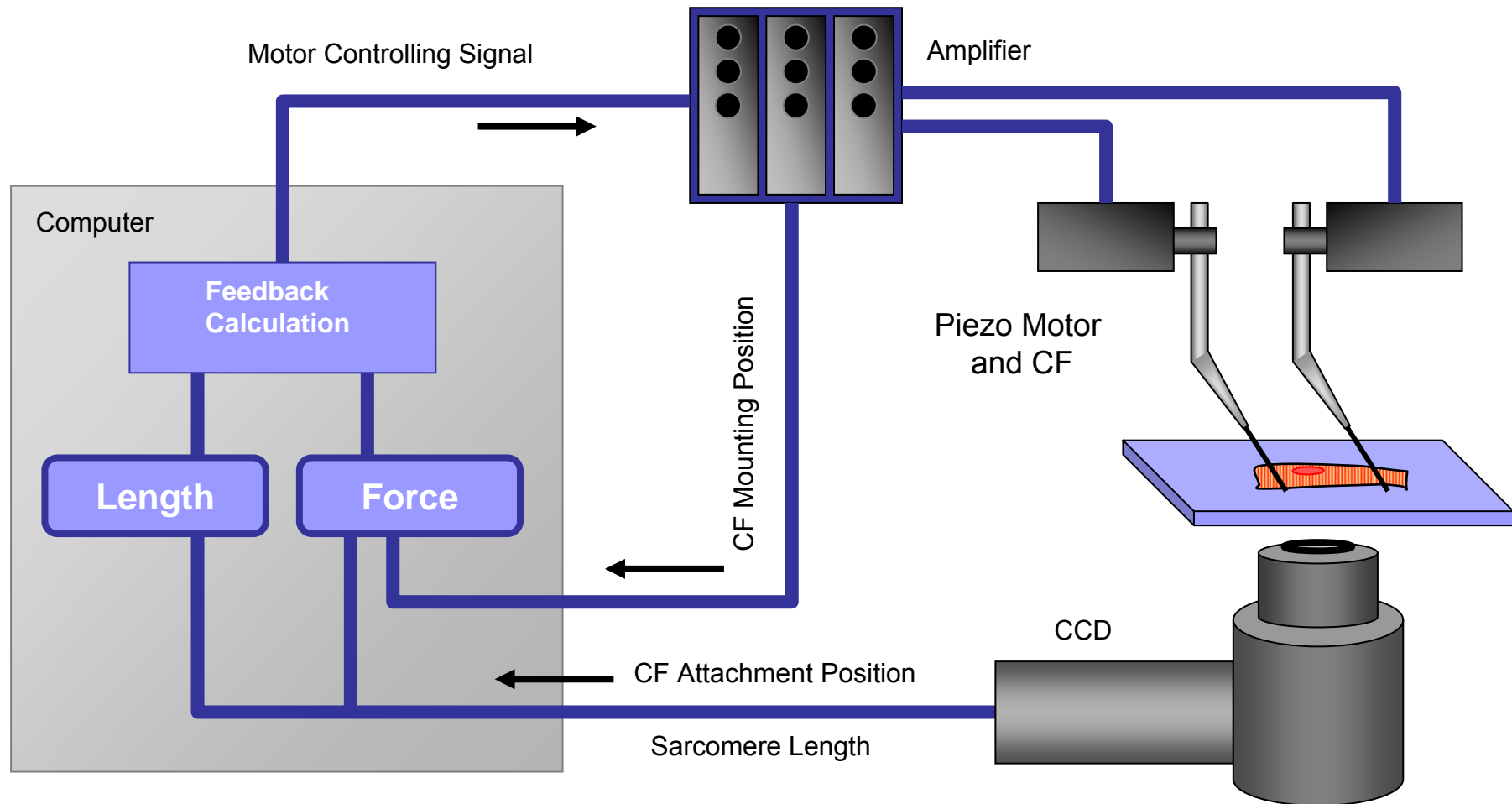
- **Cellular level:** pressure-volume loop



*Gentaro Iribe & Michiel Helmes (IonOptix)*

# Physiology – Engineering

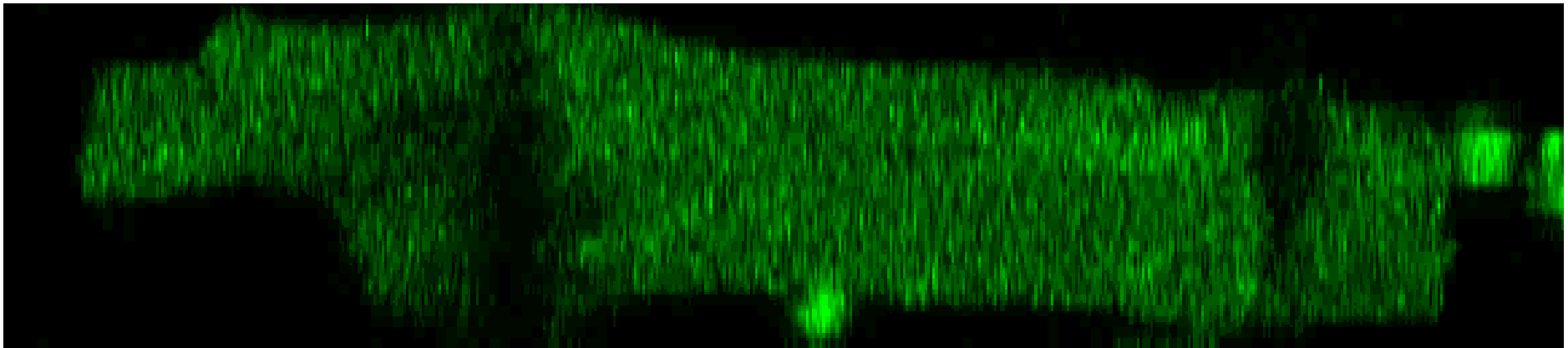
- **Cellular level: pressure-volume loop**



*Gentaro Iribe & Michiel Helmes (IonOptix)*

# Physiology – Engineering

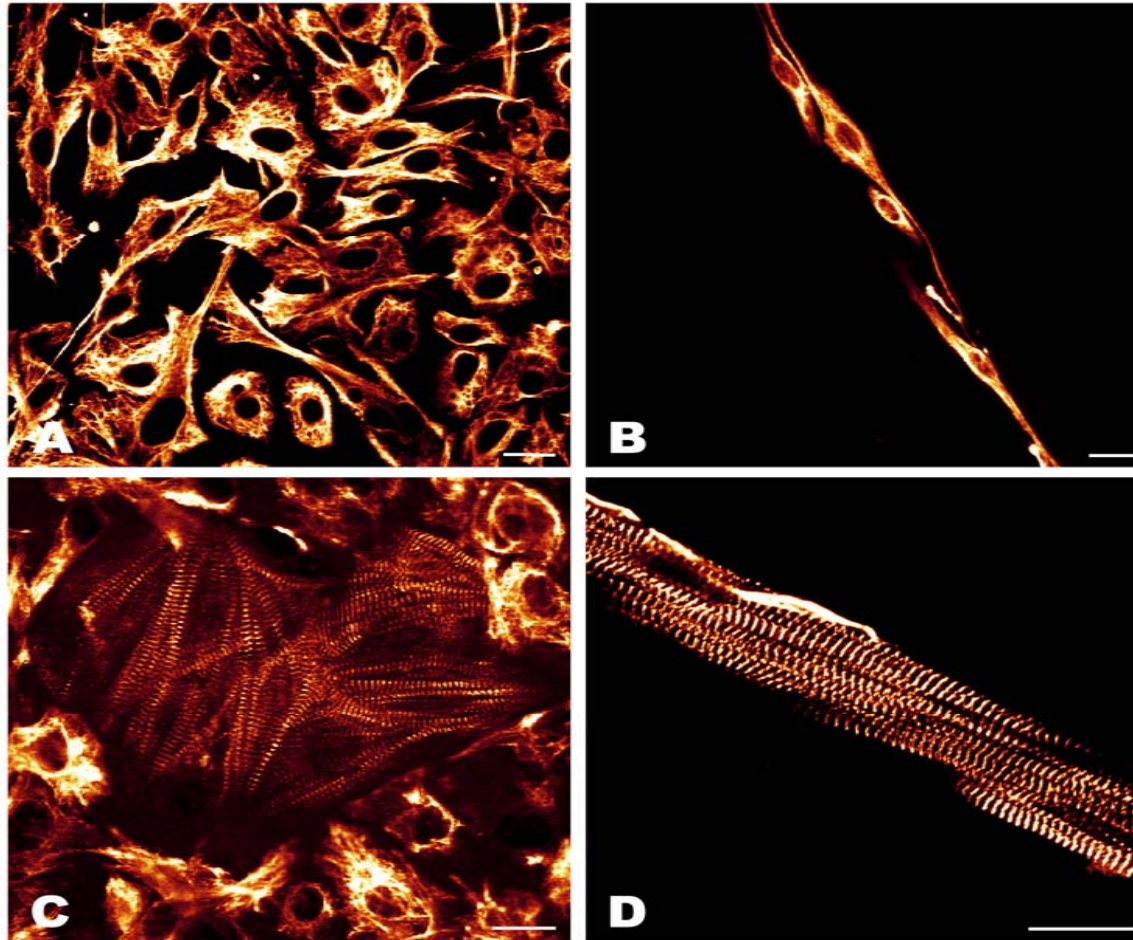
- **Cellular level:**  $\text{Ca}^{2+}$  sparks / waves



*Gentaro Iribe & Jon Lederer (Baltimore)*

# Physiology – Engineering

- **Tissue level:** structured cell culture



*Patrizia Camelliti & Andrew McCulloch (UCSD)*

# Physiology – Engineering

- **Organ level: the STICK**

S - oft  
T - issue  
I - mpact  
C - haracterisation  
K - it



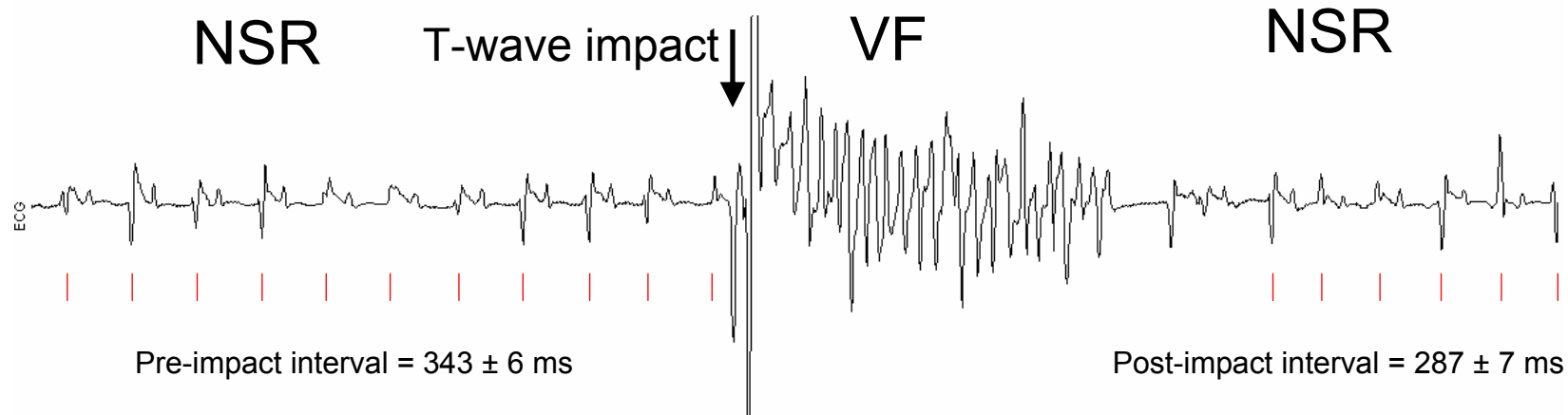
*Patricia Cooper & Christian Boulin (EMBL)*

# Physiology – Engineering

## ● Organ level: the STICK



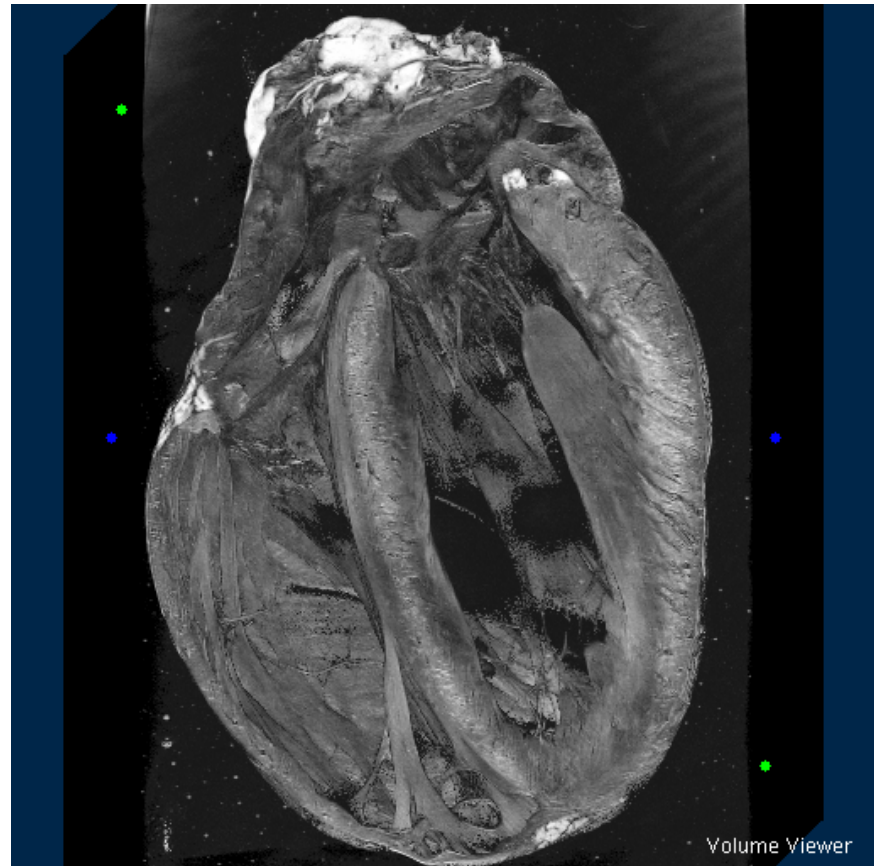
**S** - oft  
**T** - issue  
**I** - mpact  
**C** - haracterisation  
**K** - it



*Patricia Cooper & Christian Boulin (EMBL)*

# Physiology – Engineering

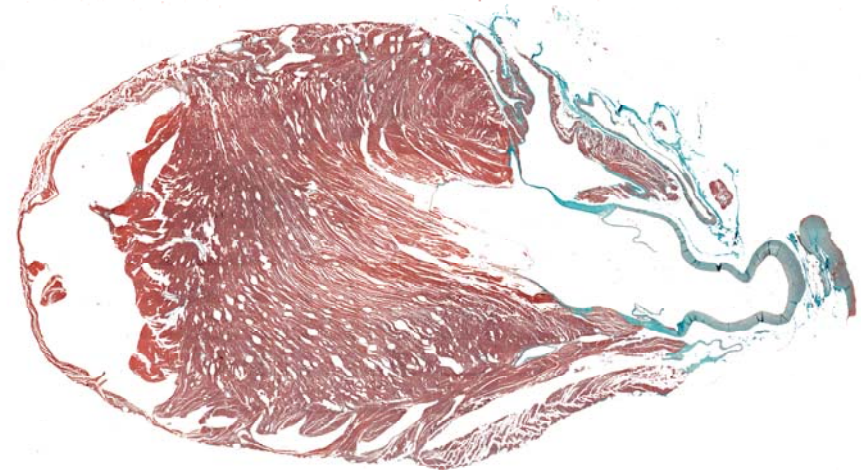
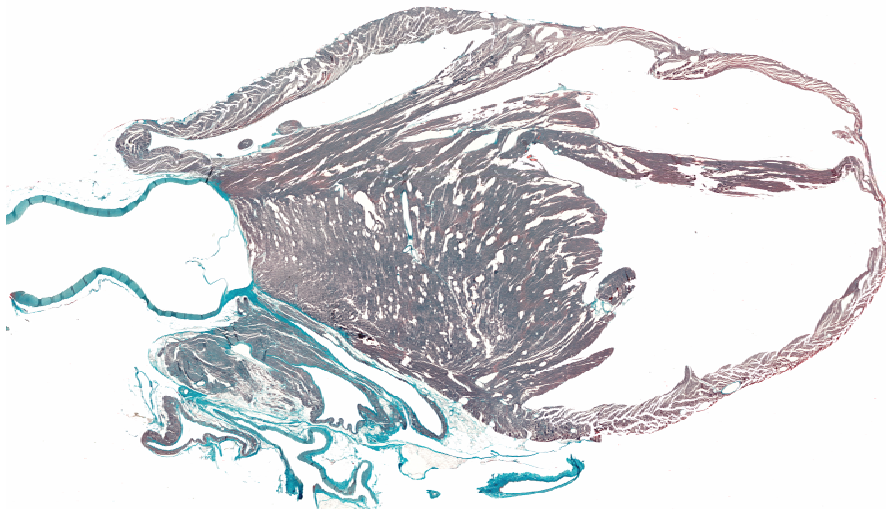
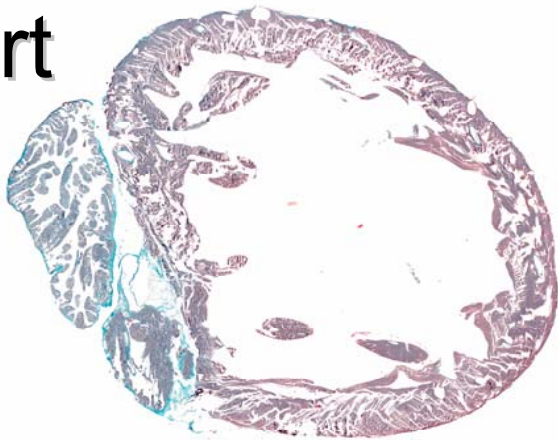
- **Organ level:** 3D reconstruction of the rabbit heart



*Rebecca Rowland, Gernot Plank (Graz) & Jürgen Schneider*

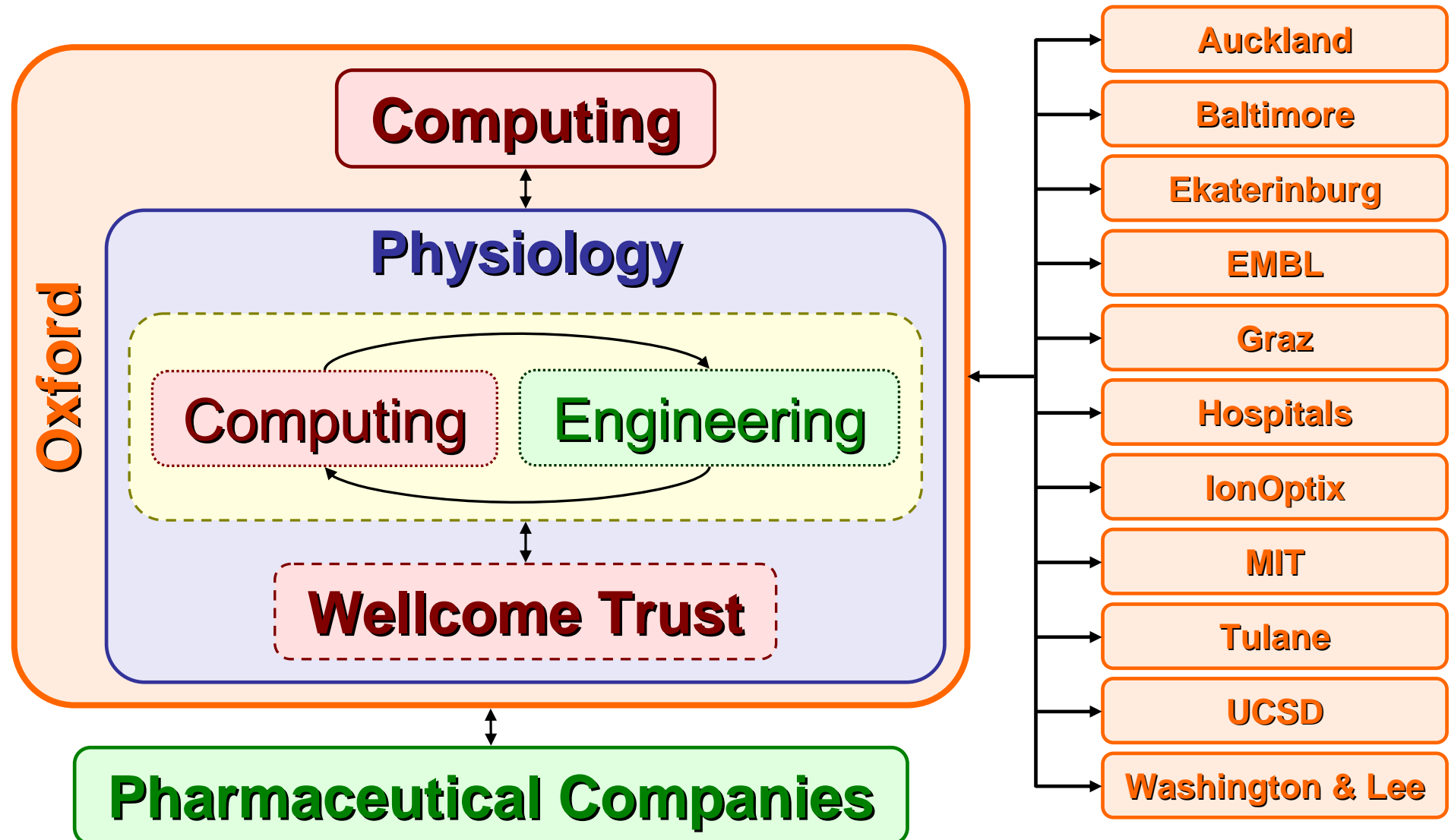
# Physiology – Engineering

- **Organ level:** 3D reconstruction of the rabbit heart



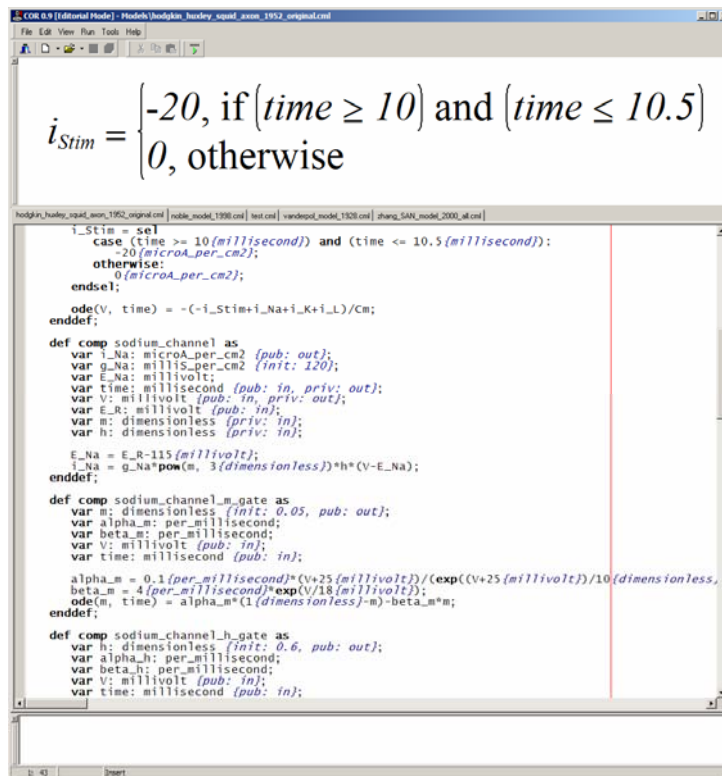
*Rebecca Rowland, Gernot Plank (Graz) & Jürgen Schneider*

# Interactions at Oxford



# Physiology – Computing

- **Software development: COR**
  - (Multi)cellular modelling environment.
  - Built around CellML.



```

i_Stim = 
$$\begin{cases} -20, & \text{if } (time \geq 10) \text{ and } (time \leq 10.5) \\ 0, & \text{otherwise} \end{cases}$$


i_Stim = sel
case (time >= 10{millisecond}) and (time <= 10.5{millisecond}):
  -20{microA_per_cm2};
otherwise:
  0{microA_per_cm2};
endcase;

ode(V, time) = -(-i_Stim+i_Na+i_K+i_L)/Cm;
enddef;

def comp sodium_channel as
var i_Na: microA_per_cm2 {pub: out};
var g_Na: millis_per_cm2 {init: 120};
var E_Na: millivolt;
var time: millisecond {pub: in, priv: out};
var V: millivolt {pub: in, priv: out};
var E_R: millivolt {pub: in};
var m: dimensionless {priv: in};
var h: dimensionless {priv: in};

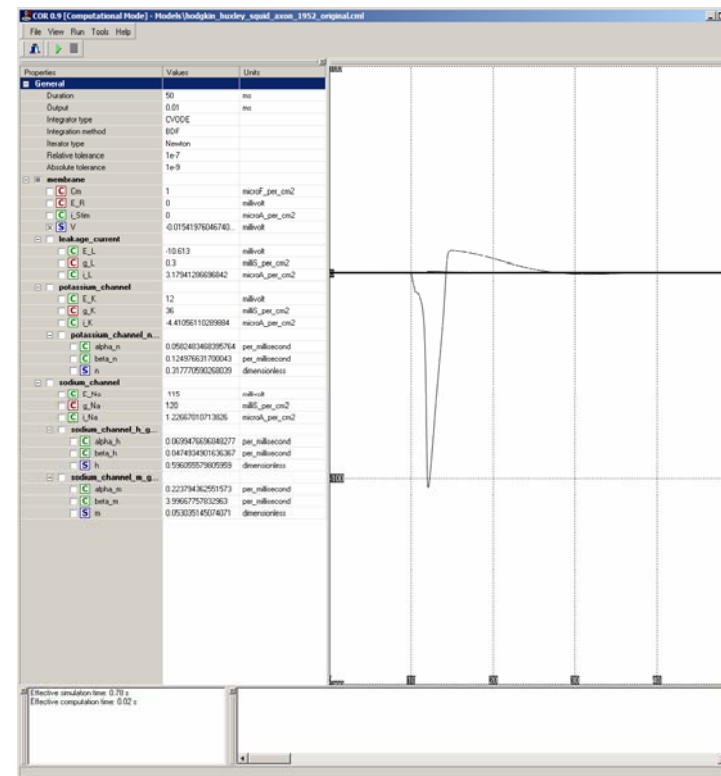
E_Na = E_R-115{millivolt};
i_Na = g_Na*pow(m, 3{dimensionless})*h*(V-E_Na);
enddef;

def comp sodium_channel_m_gate as
var m: dimensionless {init: 0.05, pub: out};
var alpha_m: per_millisecond;
var beta_m: per_millisecond;
var V: millivolt {pub: in};
var time: millisecond {pub: in};

alpha_m = 0.1{per_millisecond}*(V+25{millivolt})/(exp((V+25{millivolt})/10{dimensionless}));
beta_m = 4{per_millisecond}*exp(V/18{millivolt});
ode(m, time) = alpha_m*(1{dimensionless}-m)-beta_m*m;
enddef;

def comp sodium_channel_h_gate as
var h: dimensionless {init: 0.6, pub: out};
var alpha_h: per_millisecond;
var beta_h: per_millisecond;
var V: millivolt {pub: in};
var time: millisecond {pub: in};

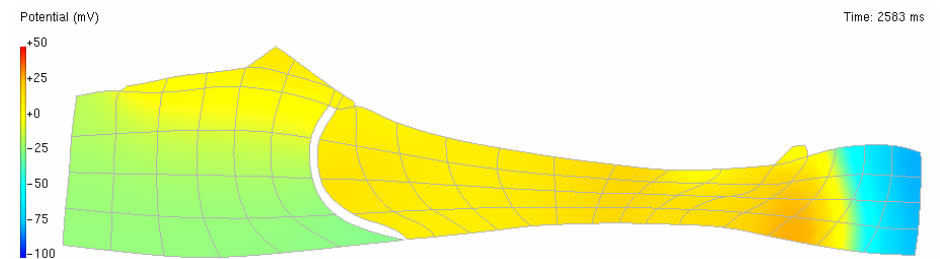
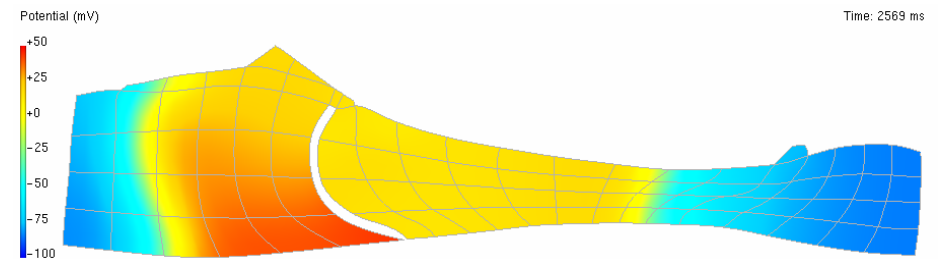
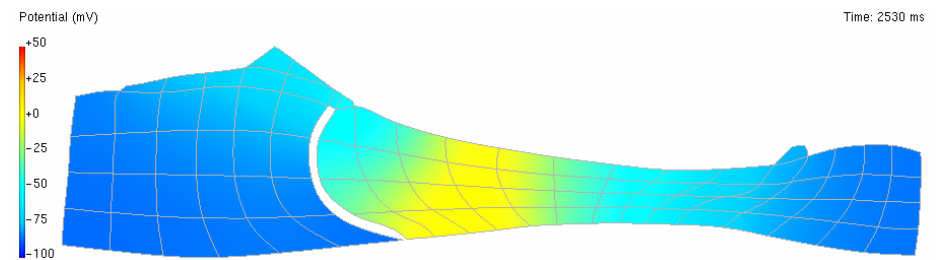
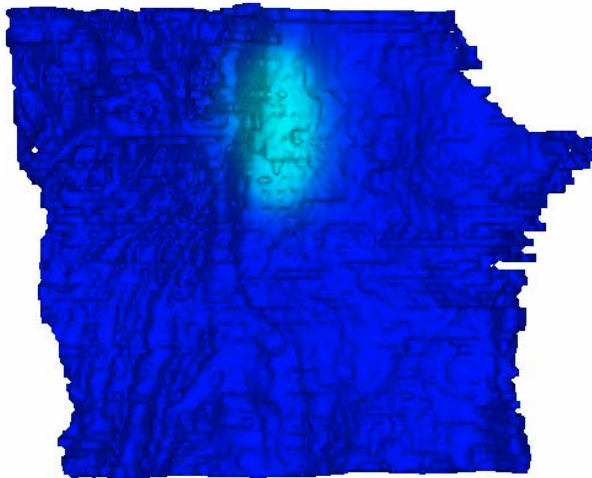
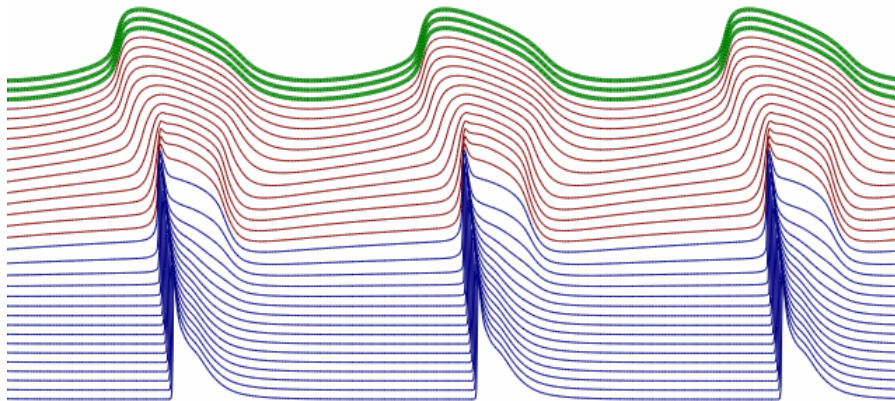
```



Alan Garny & Penny Noble

# Physiology – Computing

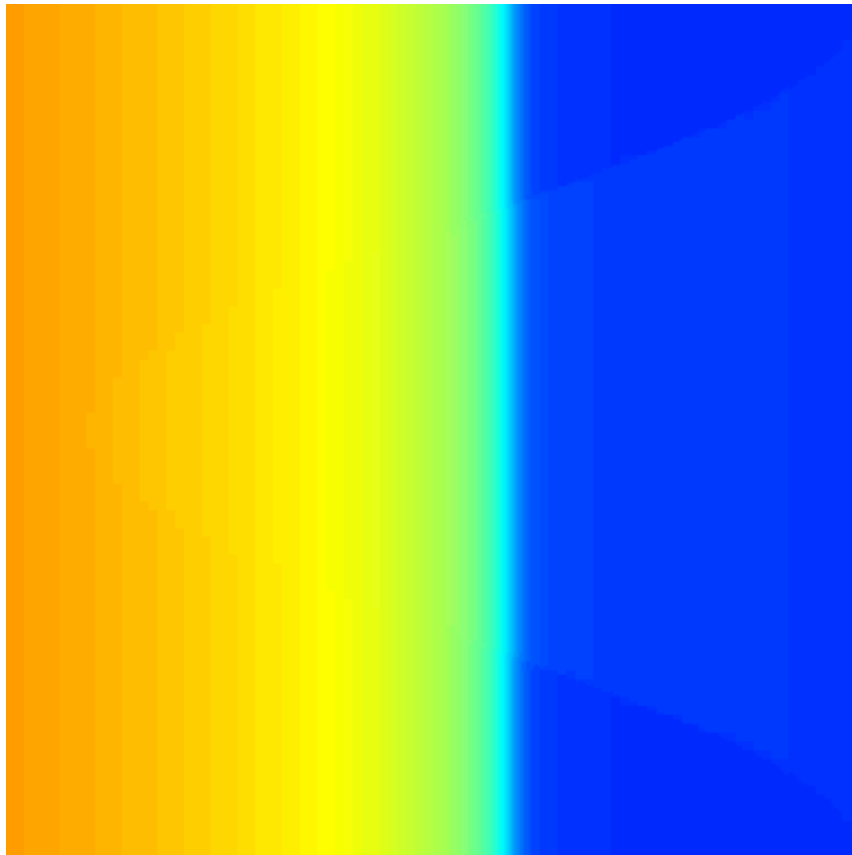
- **Sino-Atrial Node:**



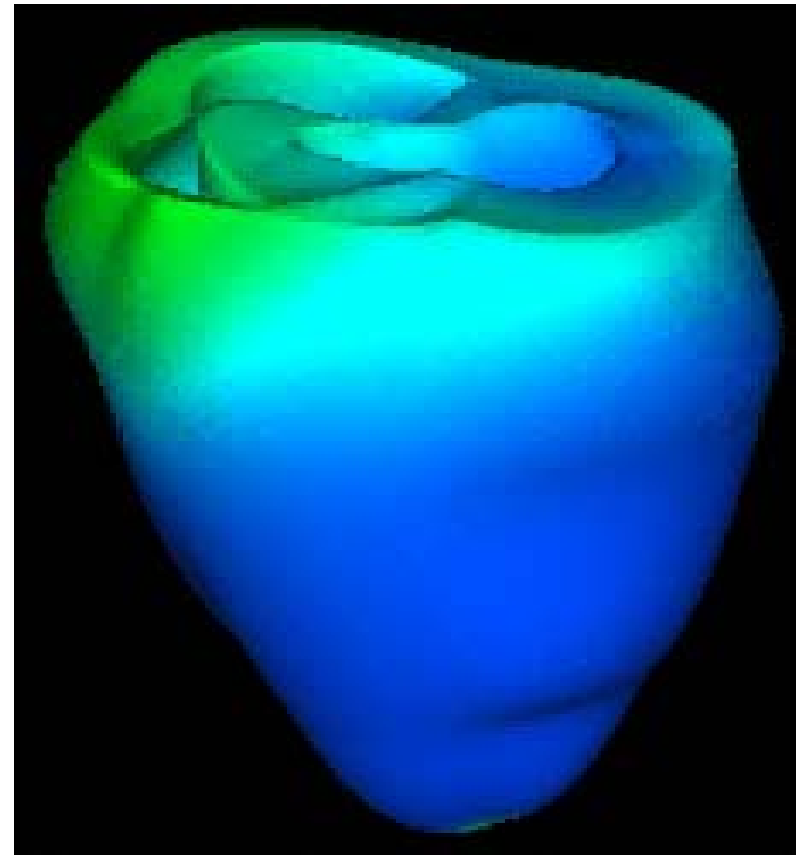
*Alan Garry*

# Physiology – Computing

- **Mechano-Electric Feedback:**

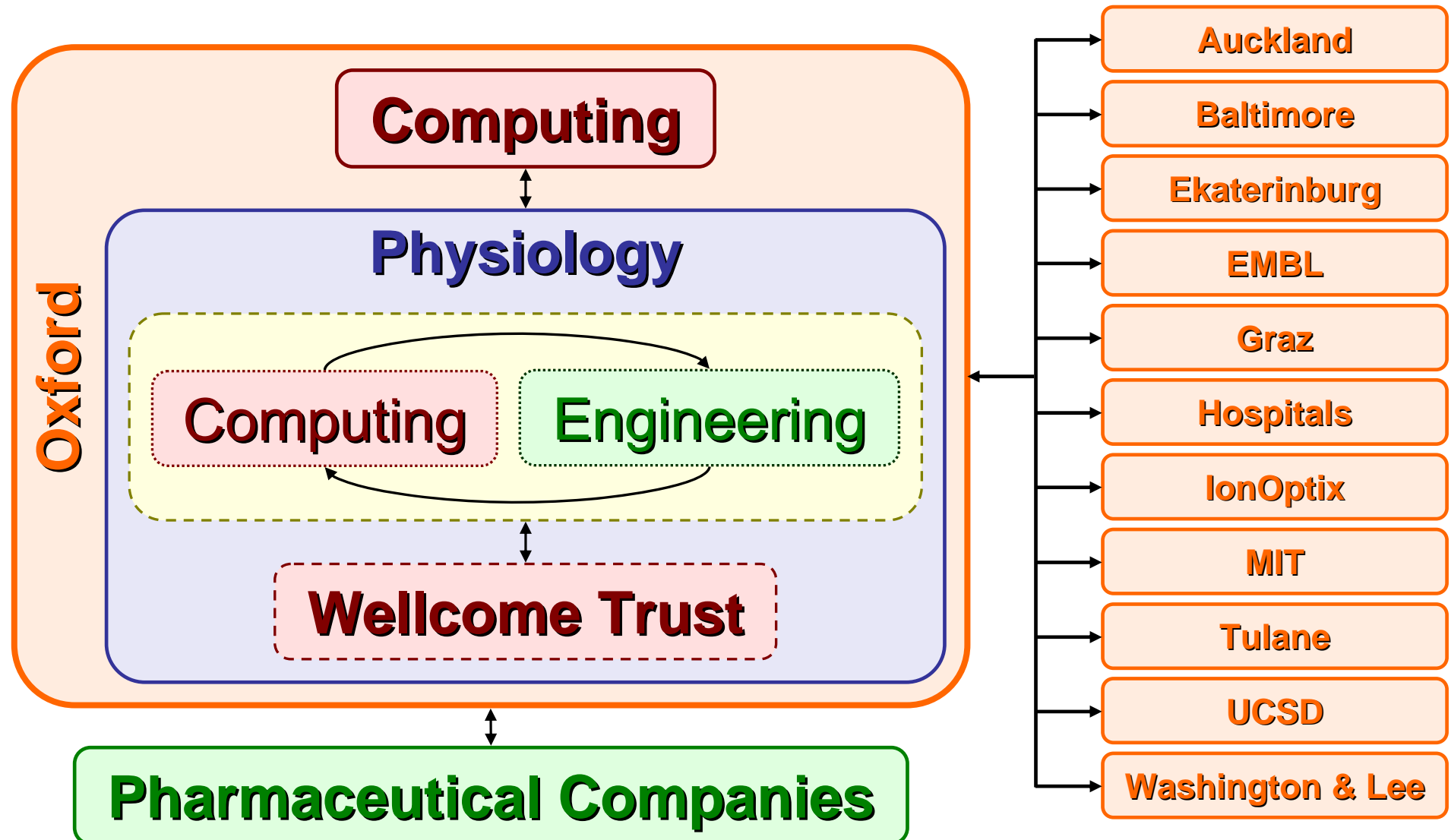


*Alan Garry*



*Natalia Trayanova (Tulane)*

# Interactions at Oxford

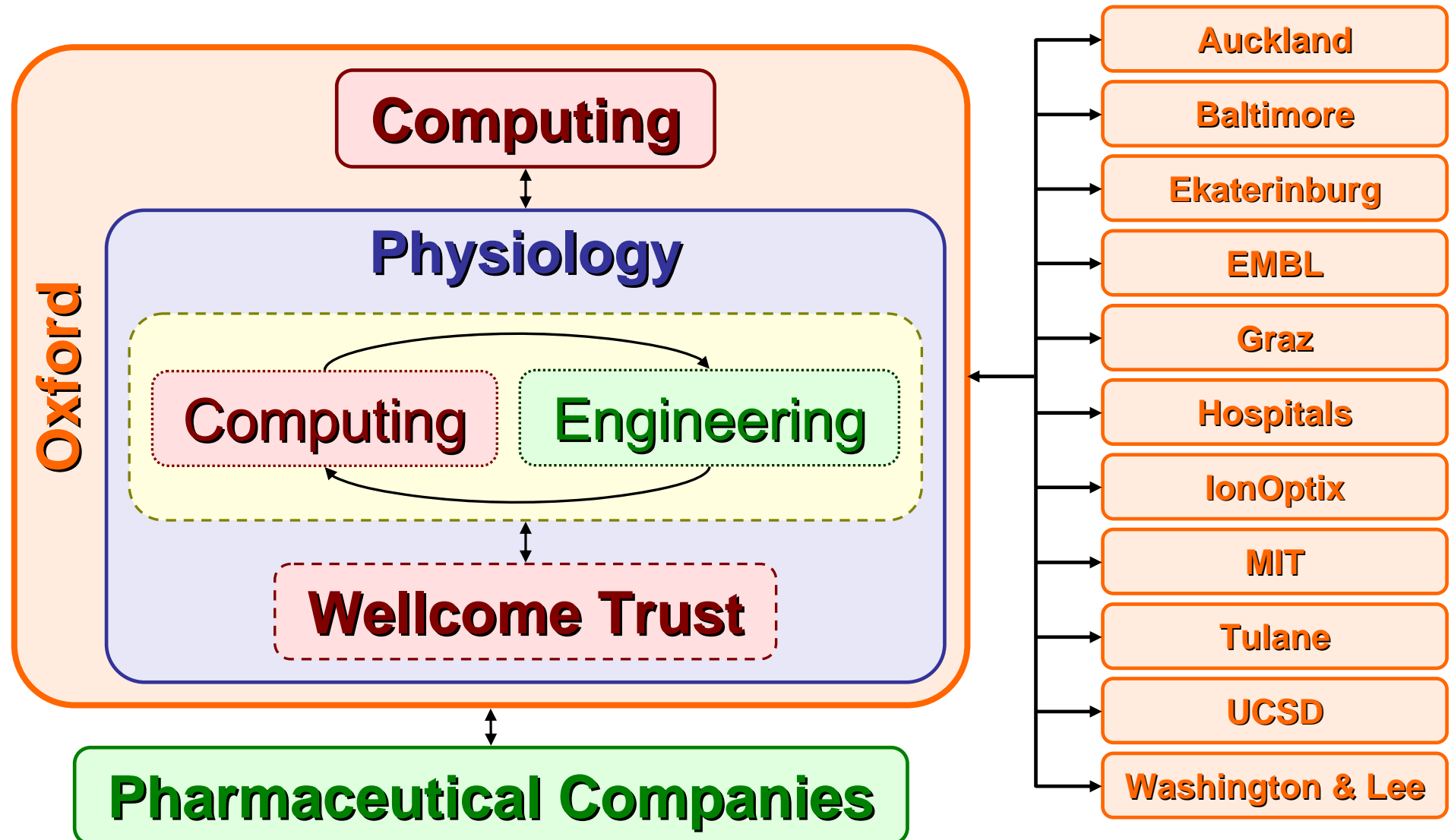


# Physiology – Wellcome Trust

- **5-year** project started in **January 2005**.
- **Proof of principle:** develop a large scale coupled computational model of the **beating heart**:
  - Incorporate models from **gene** to **whole organ** level,
  - Contributed to by **scientists around the world** in an **open manner**.
- Joint appointment of **Peter Hunter** between **Auckland** and **Oxford**.

*Peter Hunter & Chris Bradley*

# Interactions at Oxford



# Computing

- **Integrative Biology Initiative:**
  - Build a **grid-based infrastructure** for **cardiac** and **cancer** modelling,
  - Cardiac modelling: **Auckland, Calgary, Ekaterinburg, Graz, Sheffield, Tulane, UCLA, UCSD, Utrecht & Washington and Lee.**
- **Software development:** Chaste
  - **C++/PETSc/MPI** library,
  - **Extreme/Agile Prog.** (e.g. test driven).

*David Gavaghan, Jonathan Cooper, **Alan Garny**, Joe Pitt-Francis,  
Lee Momtahan & Blanca Rodriguez*

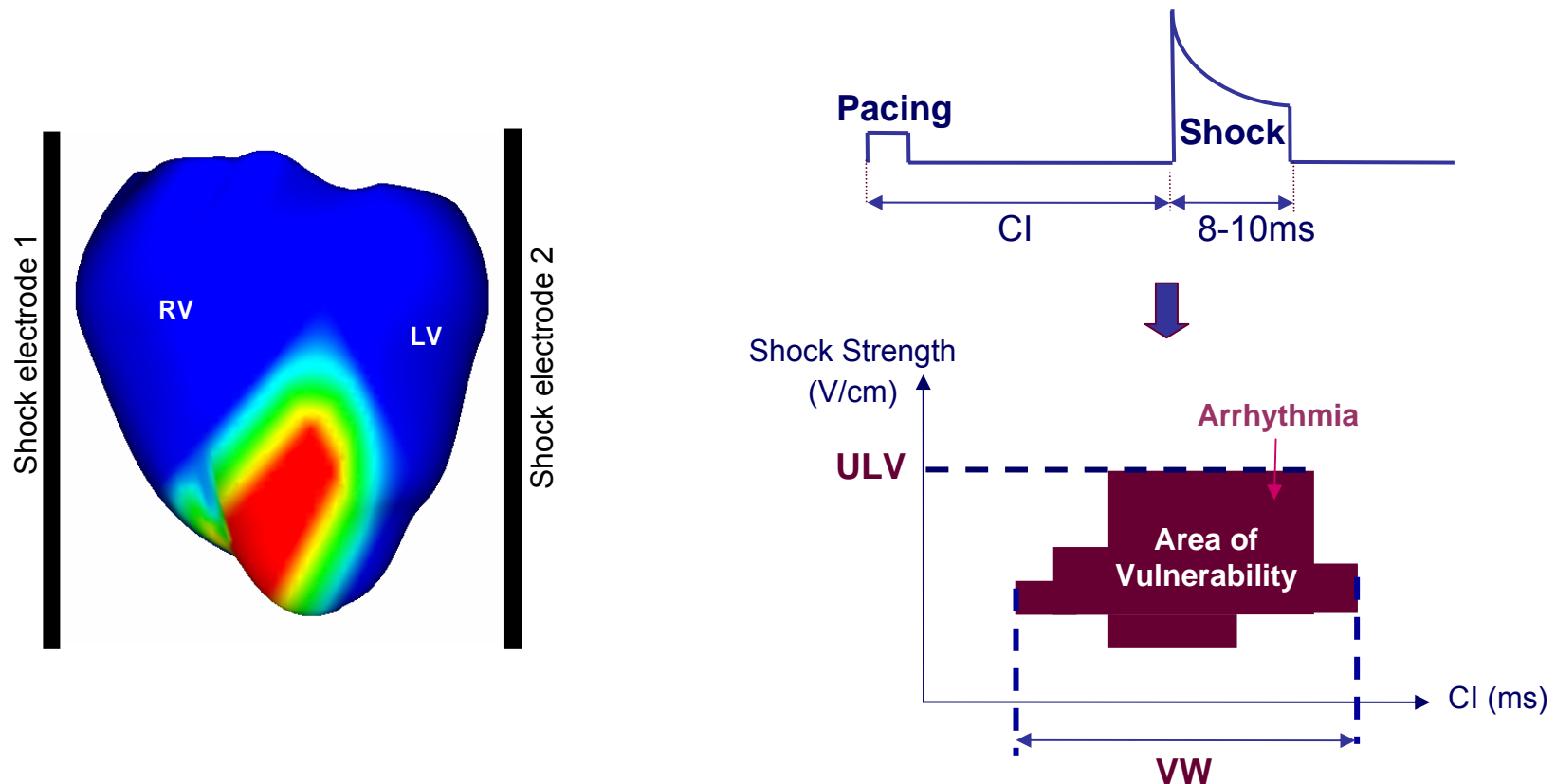
# Computing

- **Numerical techniques:**

- Compiler optimisations (Intel family of processors – SSE, SSE2; 4.4x / 2.6x),
- Lookup tables (automatically generated from CellML; 1.6x or 9.2x w/ opt.),
- Partial evaluation (1.2x or 4.9x w/ LT),
- Decoupling between  $\Delta x$  and  $\Delta t$ .

# Computing

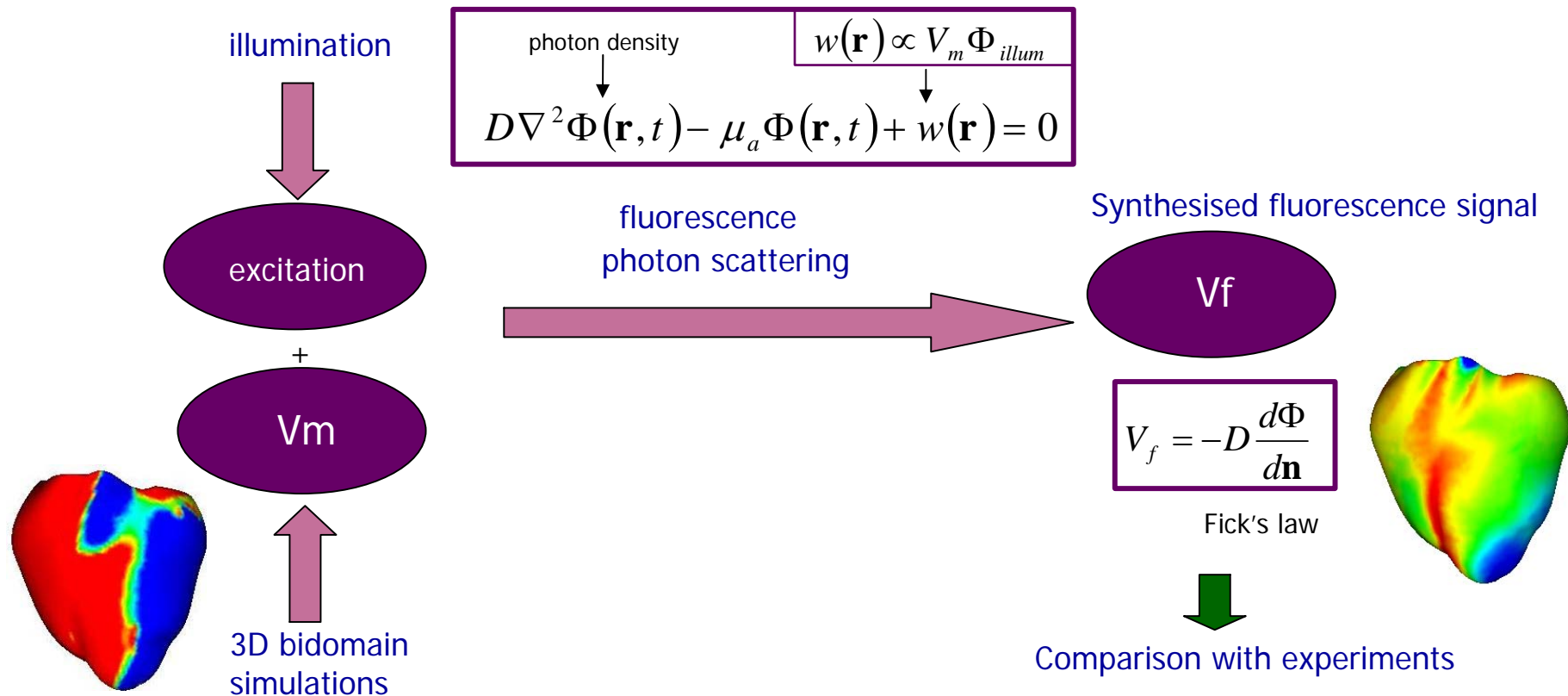
- Defibrillation during regional ischaemia



*Blanca Rodriguez, Jamey Eason (Washington & Lee) &  
Natalia Trayanova (Tulane)*

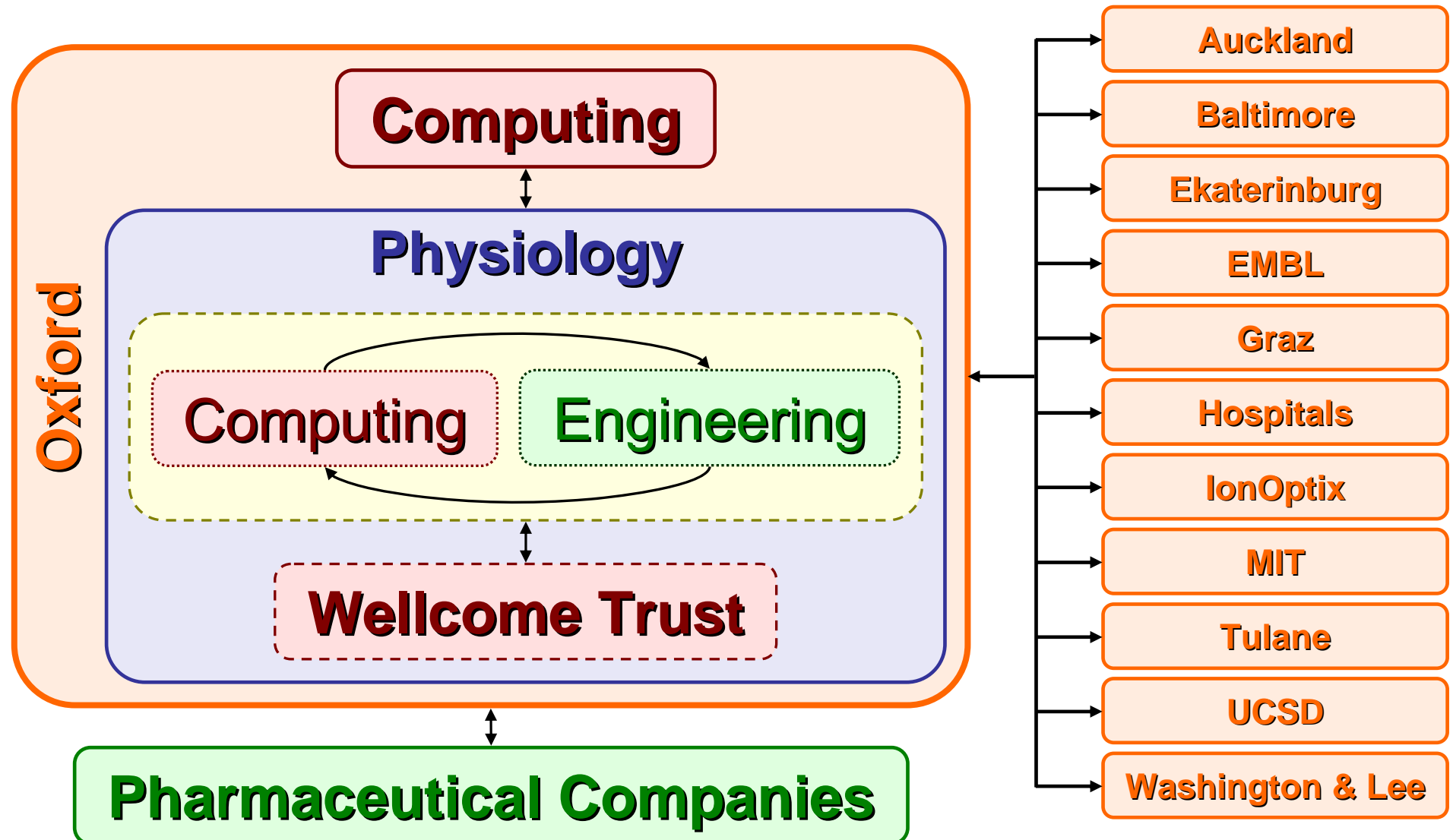
# Computing

- Optical mapping recordings synthesis



*Martin Bishop, Jamey Eason (Washington & Lee), Blanca Rodriguez, Natalia Trayanova (Tulane) & Jonathan Whiteley*

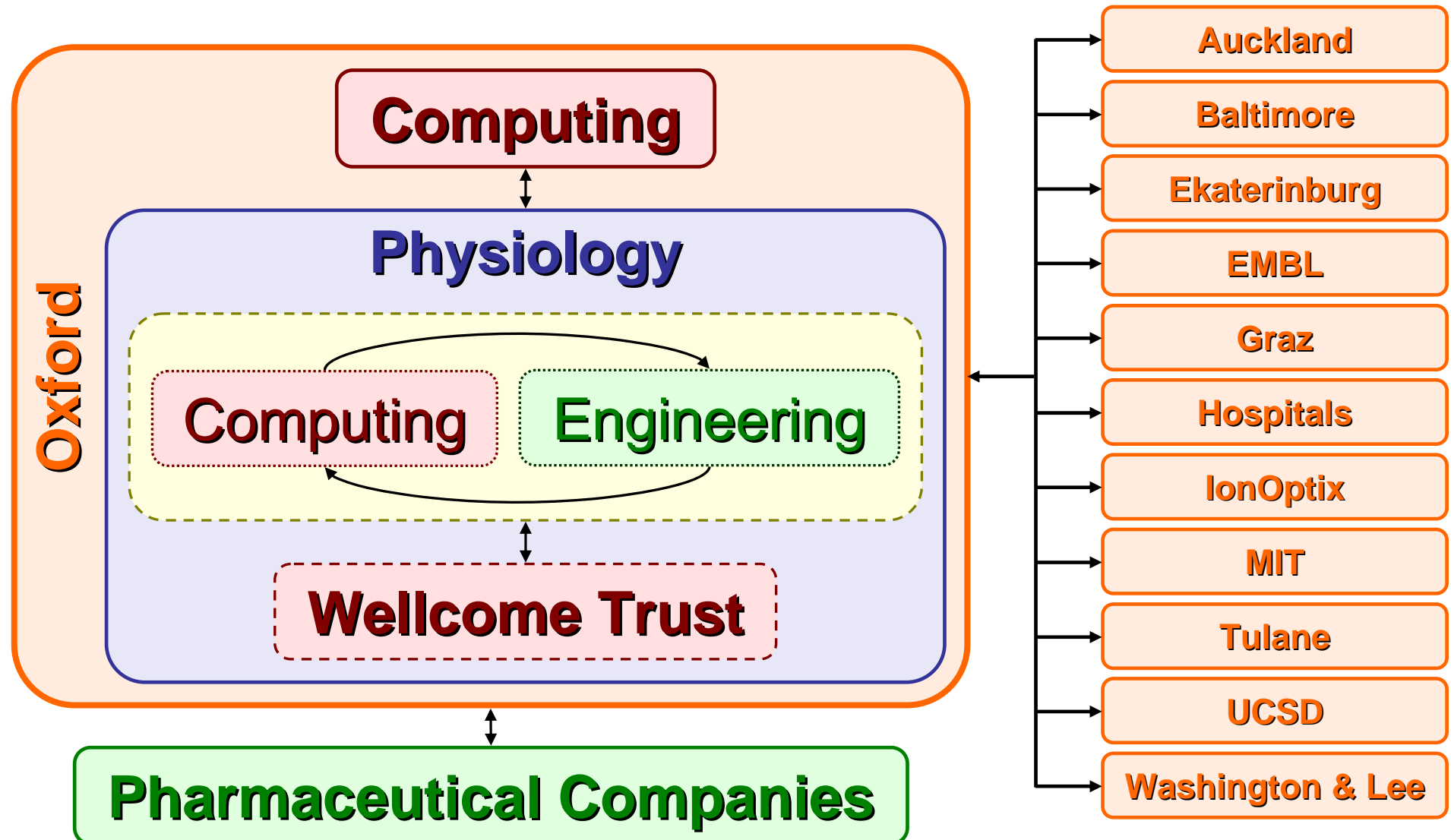
# Interactions at Oxford



# Pharmaceutical Companies

- Predict the influence of **drugs** and the consequences of **gene mutations** to achieve better and more selective markers for **arrhythmia**,
- Collaboration with **CV Therapeutics** to reconstruct **Ranolazine**, a drug that blocks  $i_{pNa}$  but not  $i_{Na}$ ,
- Collaboration with **Novartis** to reverse engineer the effects of two different compounds.

# Interactions at Oxford



# Links...

- **Physiology:**

<http://noble.physiol.ox.ac.uk/>

<http://mef.physiol.ox.ac.uk/>

<http://cor.physiol.ox.ac.uk/>

<http://www.physiome.ox.ac.uk/> (soon)

- **Computing:**

<http://www.integrativebiology.ox.ac.uk/>