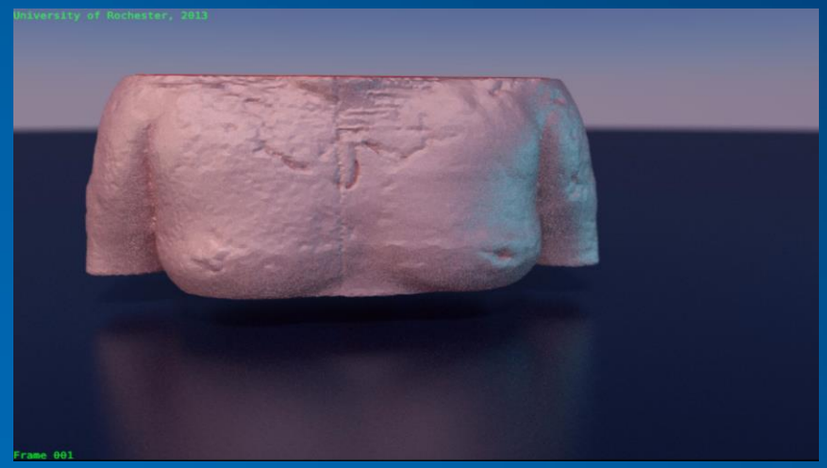
Developing a High-Resolution 3D Heart Model for Drug Safety Assays



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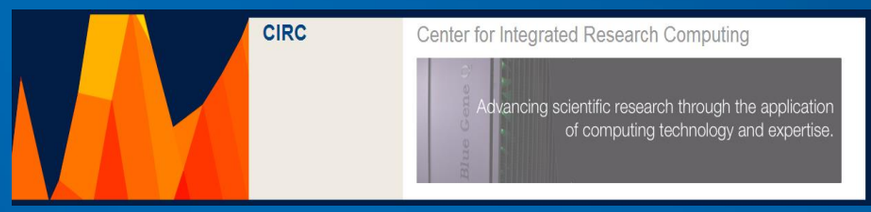
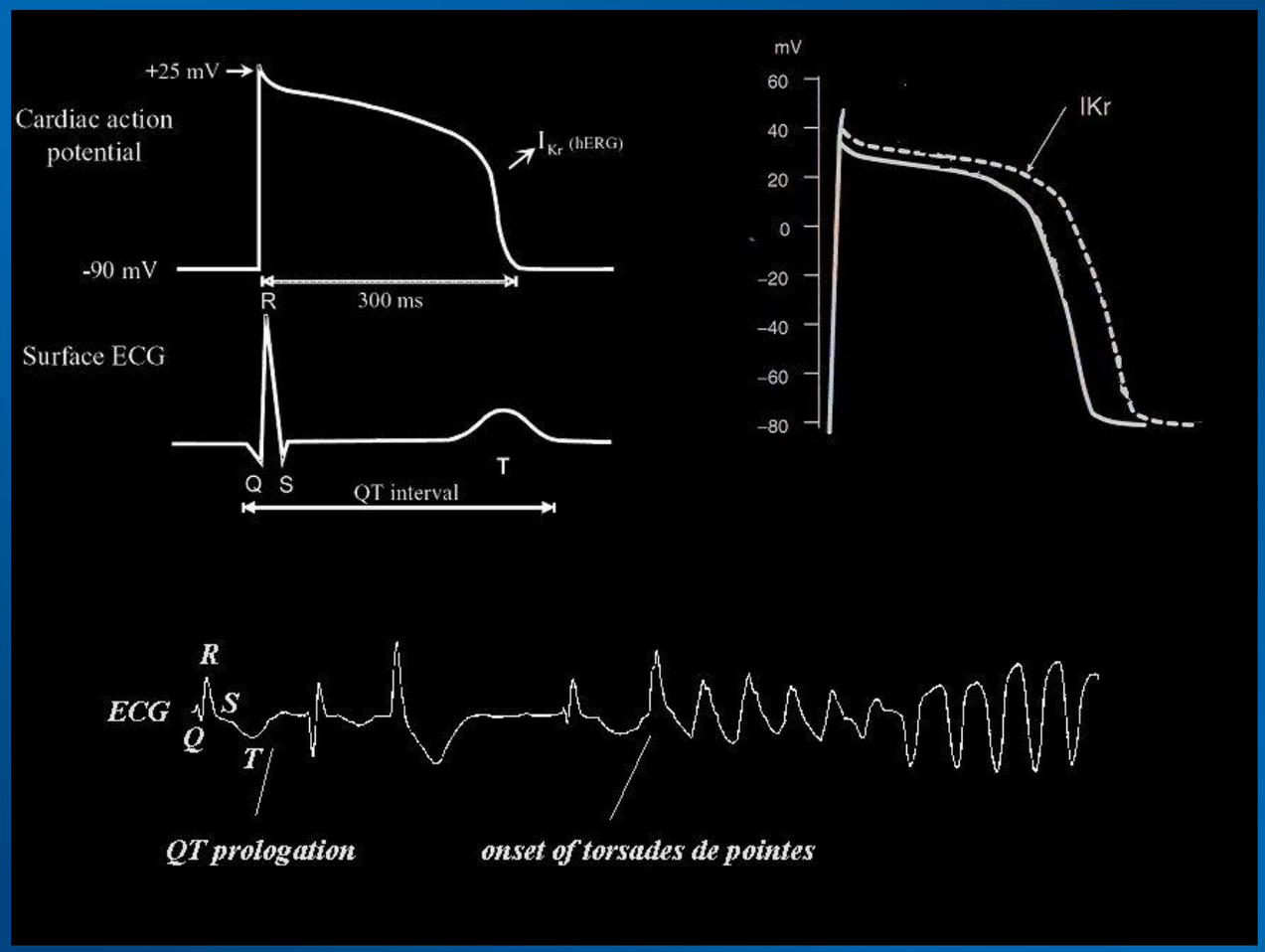


MEDICINE *of* THE HIGHEST ORDER

UNIVERSITY *of* ROCHESTER MEDICAL CENTER

QT-prolonging Drugs

Drugs associated with TdP often inhibit the rapid component of the delayed rectifier potassium current (Ikr)



Drug Cardiotoxicity

- The anti-allergic drug terfenadine was approved for clinical use in the U.S. in 1985 by the Food and Drug Administration (US FDA).

- June 1990, 25 cases of QT interval prolongation alone or in association with serious ventricular arrhythmias, or sudden death in an arrhythmic setting were reported.

- In 2004, FDA recommends the Thorough QT (TQT) studies in order to assess the propensity of new compound to have proarrhythmic effects by delaying the ventricular repolarization process of the heart.

Rationale

- QT as inadequate marker
- FDA recently expressed the need for replacing TQT studies in the next 2 to 3 years by **sensitive and more specific assays**. Computer modeling is likely to play a crucial role.

BioCentury, THE BERNSTEIN REPORT ON BIOBUSINESS AUGUST 5, 2013 PAGE A2 OF 24

Regulation,
from previous page

tal Sciences Institute (HESI) and the **Cardiac Safety Research Consortium** (CSRC) agreed.

The new assay suite would be designed to directly measure the proarrhythmia potential of compounds and thus be better suited for culling unsafe compounds than thorough QT trials (tQT) and existing preclinical assays, because neither is highly predictive of Torsades de Pointes (TdP), a

"It's my hope the stakeholders treat July 2015 as a deadline we must work together to meet in order to get a working preclinical assay in place."

Norman Stockbridge, FDA

evidence of arrhythmia in preclinical studies looking at alternative markers of TdP risk *(see BioCentury, Dec. 15, 2003)*.

Nonetheless, FDA issued an approvable letter to CV Therapeutics, asking for another trial. And about two months later, the agency held an advisory committee meeting partly because of the QT prolongation data.

CVT's presentation to the committee included data submitted to FDA on two preclinical markers of TdP — early afterdepolarization (EAD) and spatial dis-

see Biocentury, the Bernstein report on Biobusiness, vol. 21, 30, page A1-5

Cardioid Objectives

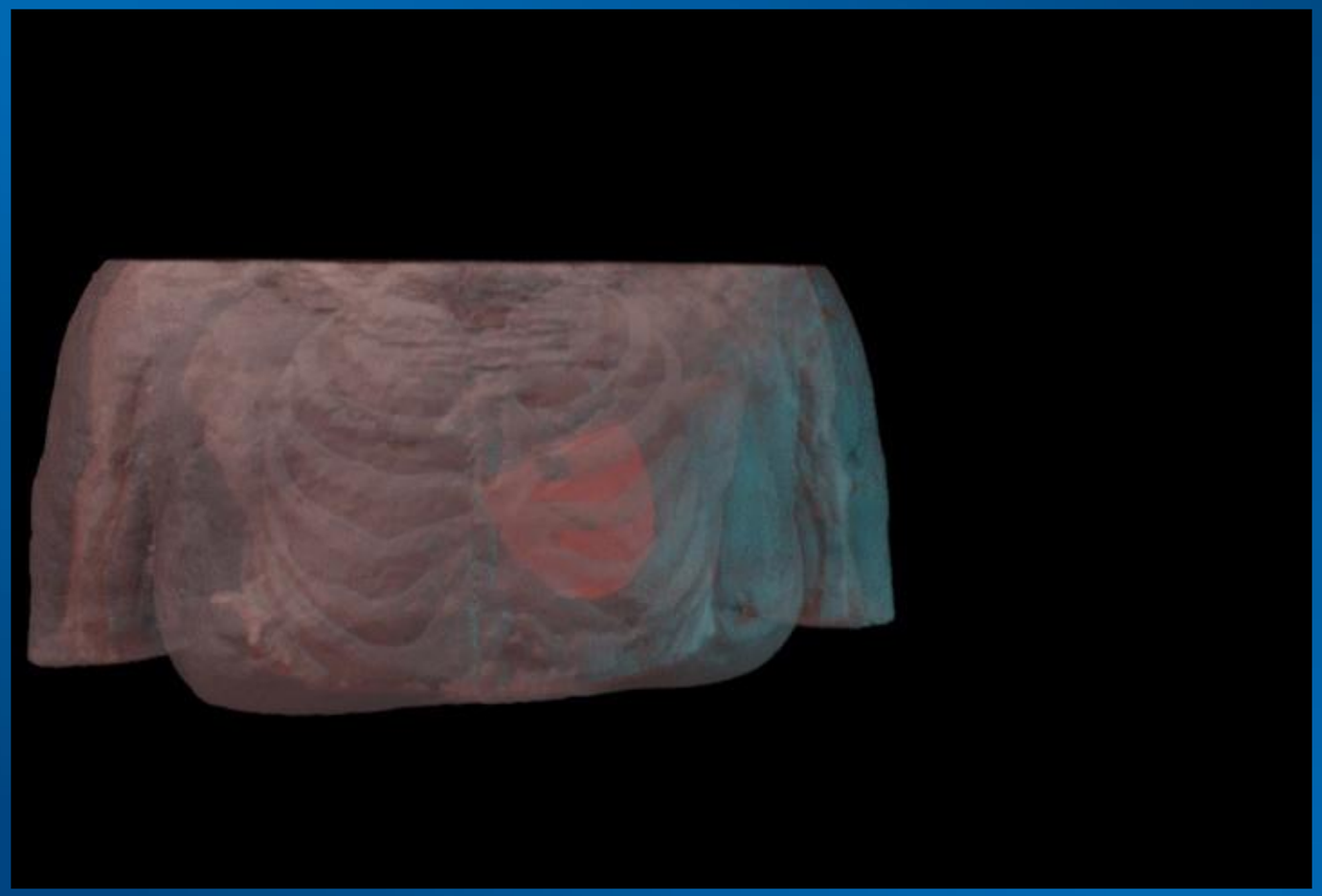
Develop a unique set of drug safety assays based on in-silico models from single cardiac cell to whole human heart/torso model using the IBM Cardioid software.

The in-silico assays will be developed, calibrated, and validated using expertise of biomedical engineers, clinicians, molecular scientists, and modelers from the University of Rochester (HRFUP, CVRI,CIRC) and IBM.

Approach

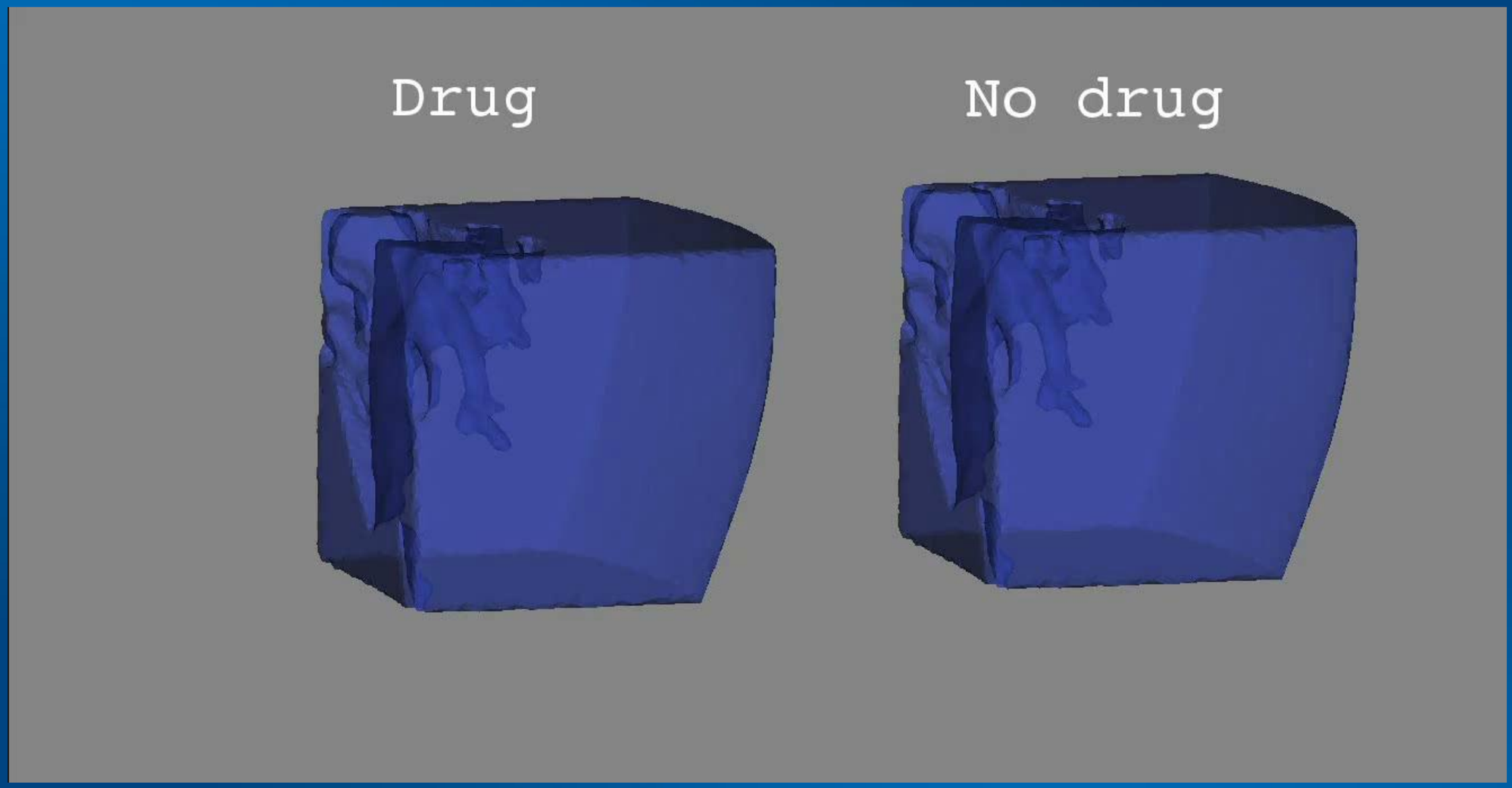
- Measurements of in-vitro drug effects in ion channel functions.
- Translate these findings into the in-silico IBM heart models.
- Tune and validate the IBM heart model by evaluating its ability to reproduce ECG changes observed in real clinical conditions.

In-silico heart/torso model



Heart and Torso model.

Ikr Blockade in-silico 3D Wedge



Simulating the effect of Ikr blockade in the cardiac wedge.

Generating Life-threatening Arrhythmias (torsades de pointes)

Conclusion & Perspectives

- We initiated a collaborative project for the calibration and validation of an in-silico human heart/torso model for drug safety assays.

- The UofR Blue Gene Q provide us with the ability to compute one cardiac beat in ~30 min. The calibration of the model will require to run a large number of iterations.

- It is planned that the resulting in-silico assay modeling will be presented to the FDA (CDER) and pharmaceutical companies for further exploitation.