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Numerical simulation of cardiac pacing devices: modeling and validation issues

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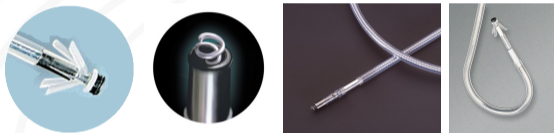
November 16, 2023



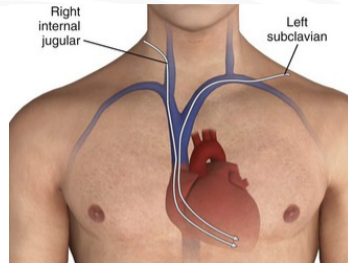
**SIM
CARDIO
TEST**

Digital transformation in Health and Care SC1-DTH-06-2020 Grant Agreement No. 101016496.

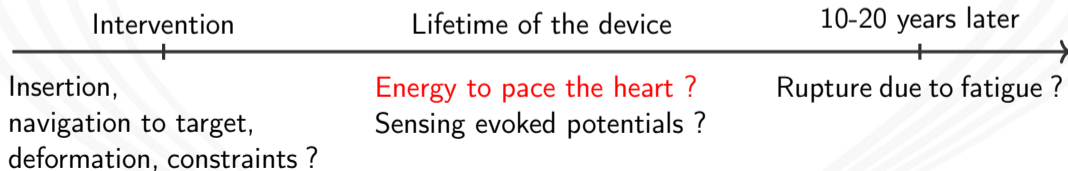
Pacemakers and electrical questions



(a) Diverse pacemaker leads



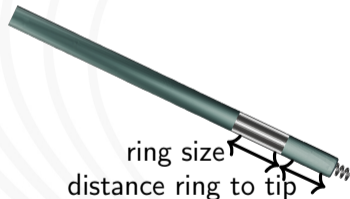
(b) Focus: bradychardia leads



Question of interest

What are the stimulation pulse characteristics (voltage amplitude in V and pulse duration in ms) required for a bradychardia lead in bipolar (tip/ring) mode to capture (stimulate) healthy cardiac tissue ?

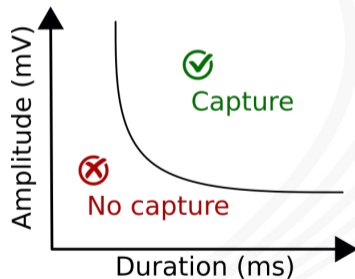
Context: threshold test in animal experiments. Influence of the design of the lead, like geometry and contact properties ?



Computer model
and simulation

Verification and
validation

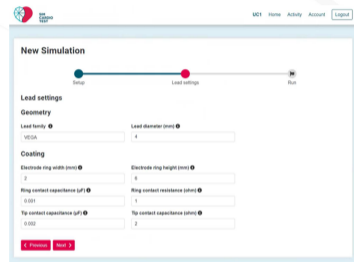
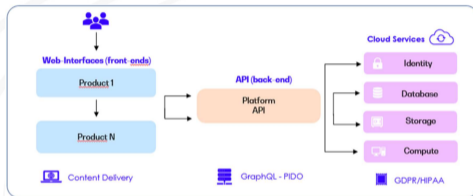
Input: design parameters



Output: Lapicque curve

Web-based computational platform

Ideal objective: run trials on a web based platform, and obtain *credible results*

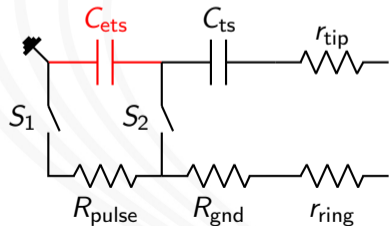
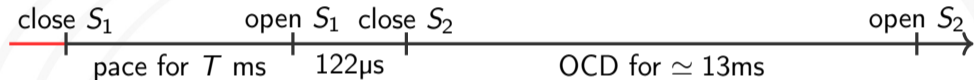


Credible according to VV40¹ : QoI, Cou, Verification, Validation. . .

¹40-2018, *Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices*.

Time course of an electrical pulse

- 1 **Pacing:** for duration T (ms), with charge Q (eq. V)
- 2 **Interruption (switches):** $122\mu\text{s}$
- 3 **Output Capacitor Discharge (OCD):** $\simeq 13\text{ms}$



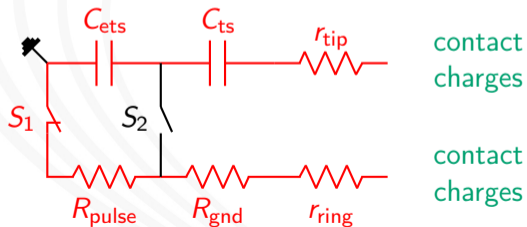
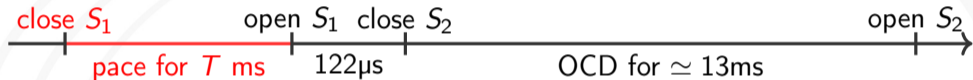
contact
?

contact
?

electrolytic bath \rightarrow bench exp.
excitable tissue \rightarrow animal exp.

Time course of an electrical pulse

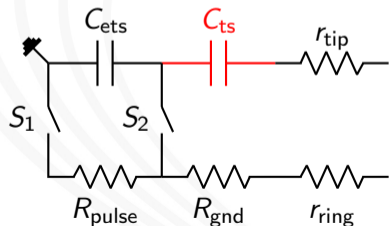
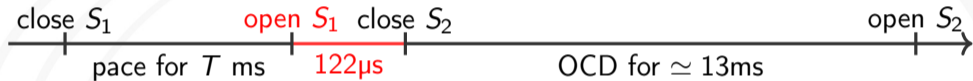
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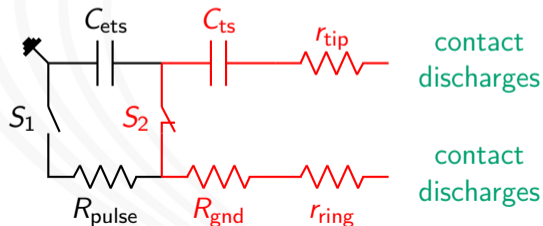
contact
discharges

contact
discharges

electrolytic bath \rightarrow bench exp.
excitable tissue \rightarrow animal exp.

Time course of an electrical pulse

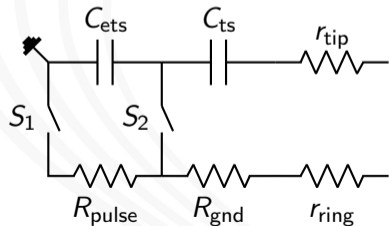
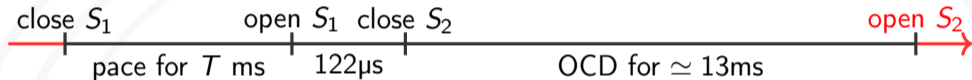
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electrolytic bath \rightarrow bench exp.
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Time course of an electrical pulse

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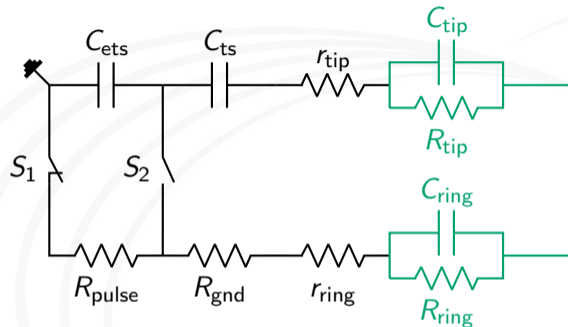


contact
?

contact
?

electrolytic bath \rightarrow bench exp.
excitable tissue \rightarrow animal exp.

Contact impedance model



electrolytic bath → bench exp.
excitable tissue → animal exp.

- At pacing, creation of a “double layer” impedance
- Boundary layer related to the Debye length
- Literature is huge²

Parallel R-C equivalent circuit

²Grimnes and Martinsen, *Bioimpedance and Bioelectricity Basics – Third Edition*.

Bath experiment / model

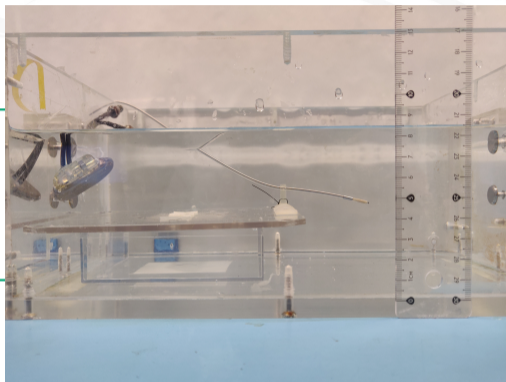
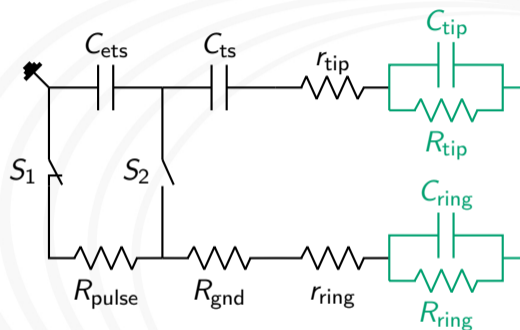
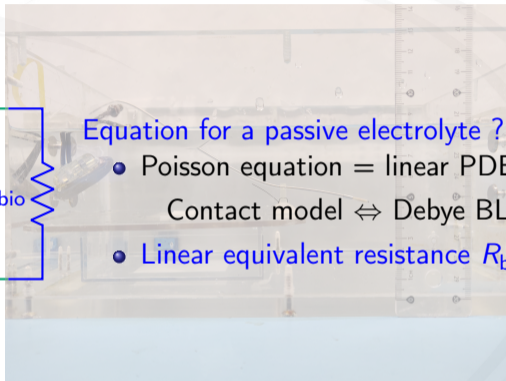
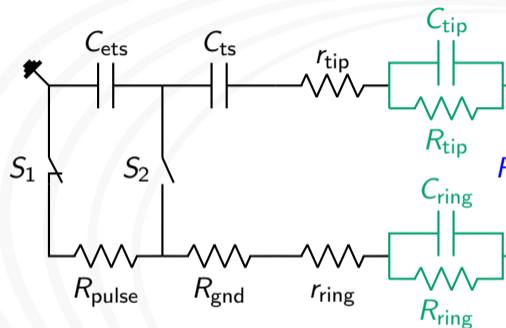


Figure: Passive bath \rightarrow def of contact model and parameter identification

Bath experiment / model

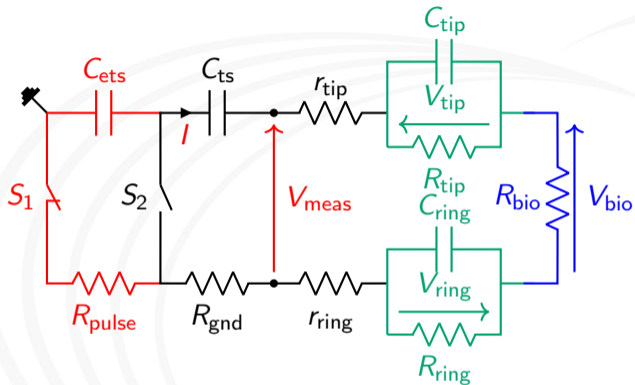


Equation for a passive electrolyte ?

- Poisson equation = linear PDE
- Contact model \Leftrightarrow Debye BL
- Linear equivalent resistance R_{bio}

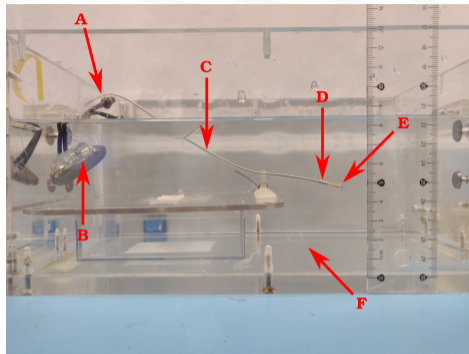
Figure: Passive bath \rightarrow def of contact model and parameter identification

The passive bath model



$$R_{\text{tot}} = R_{\text{pulse}} + R_{\text{gnd}} + r_{\text{ring}} + r_{\text{tip}} + R_{\text{bio}}$$

$$\frac{1}{C_{\text{tot}}} = \frac{1}{C_{\text{ets}}} + \frac{1}{C_{\text{ts}}} + \frac{1}{C_{\text{tip}}} + \frac{1}{C_{\text{ring}}}$$

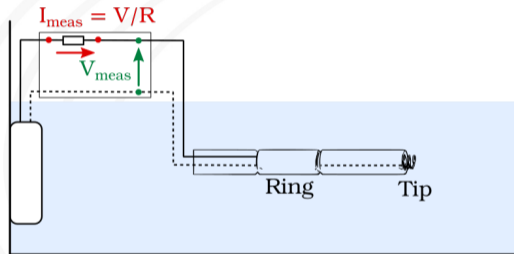


$$\frac{dl}{dt} + \frac{1}{\tau} l = \frac{1}{R_{\text{tot}}} \left(\frac{V_{\text{tip}}}{\tau_{\text{tip}}} + \frac{V_{\text{ring}}}{\tau_{\text{ring}}} \right)$$

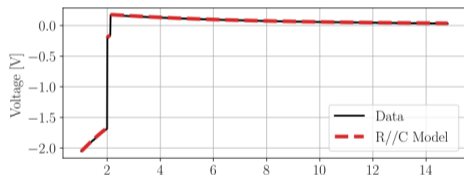
$$\frac{dV_i}{dt} + \frac{V_i}{\tau_i} = \frac{I}{C_i}, \quad i \in \{\text{tip}, \text{ring}\}$$

The passive bath experiments

- MICROPORT CRM BOREA pacemaker + VEGA leads
- Saline solution measured at $\sigma = 2.85\text{mS/cm}$



(a) Bath experiment



(b) Measured / model voltage V_{meas}

- 9 datasets: $(0.25, 0.5, 1) \text{ ms} \times (1, 2, 4) \text{ V}$

Method to calibrate the contact parameters

- Bath equivalent resistance computed from the initial data ($V_{\text{tip}} = V_{\text{ring}} = 0$):

$$R_{\text{bio}} = \frac{V_{\text{meas}}^*(t=0)}{I^*(t=0)} - r_{\text{tip}} - r_{\text{ring}}$$

- 4 parameters (device components are known):

$$\theta = (R_{\text{tip}}, R_{\text{ring}}, \tau_{\text{tip}} := R_{\text{tip}} C_{\text{tip}}, \tau_{\text{ring}} := R_{\text{tip}} C_{\text{tip}})$$

- Cost function weighted by step $s \in \{\text{pulse, interruption, OCD}\}$

$$J(\theta) = \sum_s \omega_s \mathbb{1}_s(t) \left(\frac{|V_{\text{meas}}(\theta) - V_{\text{meas}}^*|_{\ell^2}}{|V_{\text{meas}}^*|_{\ell^2}} + \frac{|I(\theta) - I^*|_{\ell^2}}{|I^*|_{\ell^2}} \right), \quad \sum_s \omega_s = 1$$

- L-BFGS-B from Python Scipy, restricted to a subset of \mathbb{R}^4
 - ▶ ODE solved semi-analytically (i.e. no approx. error)
 - ▶ First step in Log scale, $R \in (1, 1 \times 10^5)$, $\tau \in (1 \times 10^{-6}, 1)$
- 1 optimisation for each dataset \rightarrow 9 parameter sets

Calibration results – contact parameters

$$R_{\text{ring}} = 26.0 \pm 1.77\Omega, \quad \tau_{\text{ring}} = 54.8 \pm 6.93\mu\text{s}$$

$$R_{\text{tip}} = 4.0 \pm 2.0\text{k}\Omega, \quad \tau_{\text{tip}} = 50 \pm 24\text{ms}$$

Impedance measured by the pacemaker: 940 Ω

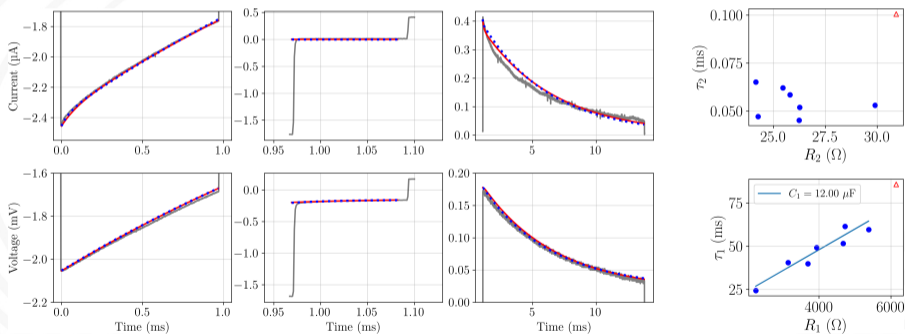


Figure: Current and voltage in each step, measures and model (left), and parameters (right)

Tissue experiment / model

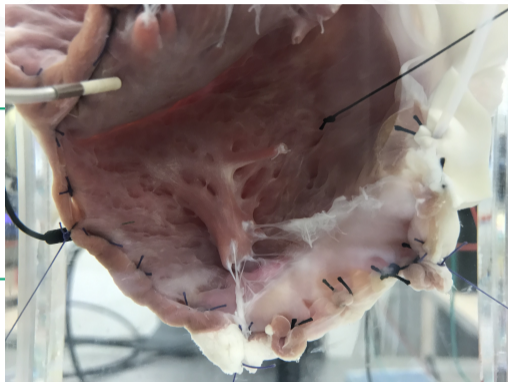
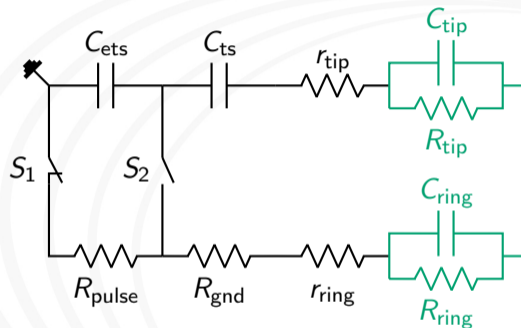
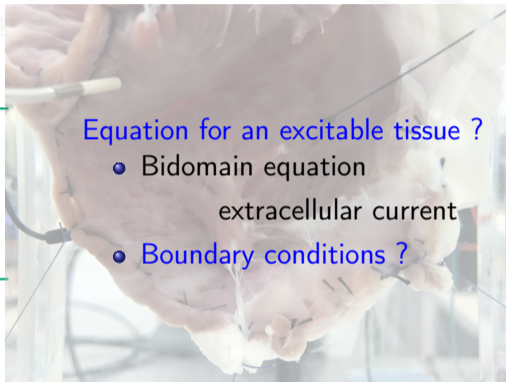
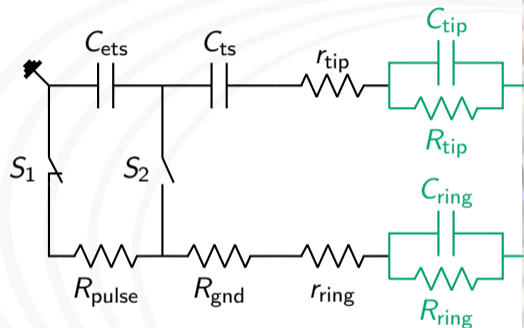


Figure: Animal experiment → validation data

Tissue experiment / model



Equation for an excitable tissue ?

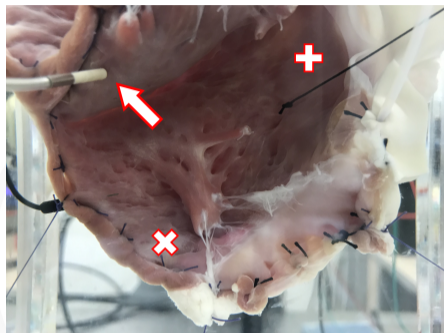
- Bidomain equation

extracellular current

- Boundary conditions ?

Figure: Animal experiment → validation data

Threshhold detection tests in animal experiments

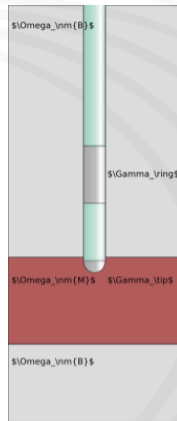
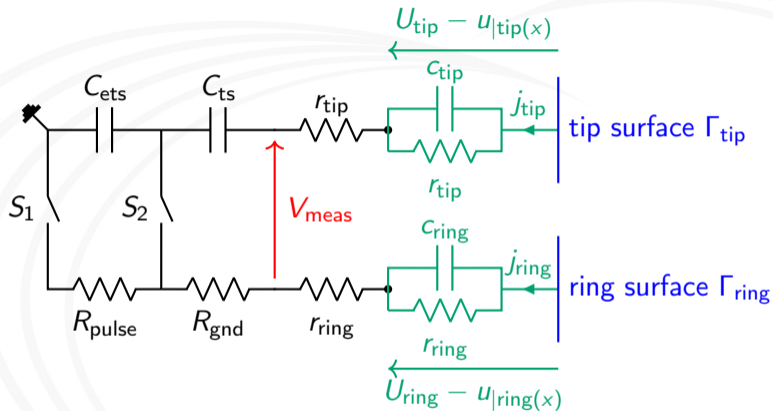


- Ventricular wedge preparation, 2 sheeps (now 3)
- 3 sites: apex (X), septum (\rightarrow), base (+)
- screw fully deployed, perpendicular
- Recording of V_{meas}^* , like in the bath
- Recording of distant EGMs with needle electrodes
- Optical signals + 9.4T MRI

Automatic threshold search by the pacemaker:

- For a fixed duration T (ms) – 5 pulses at 1.5 Hz
- Decrease voltage to locate the interval : last capturing \rightarrow first non capturing
- Capture is decided by the pacemaker, and controlled through EGMs

Bidomain coupled to the pacemaker – CEM³



$$j_i = -\sigma \nabla u \cdot n_i = c_i \partial_t (U_i(t) - u|_{\Gamma_i}(t, x)) + \frac{1}{r_i} (U_i(t) - u|_{\Gamma_i}(t, x)), \quad i \in \{\text{tip}, \text{ring}\}$$

³Somersalo, Cheney, and Isaacson, “Existence and Uniqueness for Electrode Models for Electric Current Computed Tomography”.

Complete system of equations

$$\tau_{\text{tip}} \frac{dU_{\text{ring}}}{dt} + U_{\text{ring}} = \tau \frac{dU_{\text{tip}}}{dt},$$

$$\tau_{\text{tip}} = r_{\text{tip}} C \ll \tau = RC,$$

$$R = R_{\text{pulse}} + R_{\text{gnd}} + r_{\text{ring}},$$

$$\frac{1}{C} = \frac{1}{C_{\text{ets}}} + \frac{1}{c_{\text{ts}}}$$

$$-\operatorname{div}(\sigma_i \nabla u_i) = -c_m \partial_t v_m - I_{\text{ion}}(v_m, h) \quad \text{in } \Omega_M$$

$$-\operatorname{div}(\sigma \nabla u) = \begin{cases} c_m \partial_t v_m + I_{\text{ion}}(v_m, h) & \text{in } \Omega_M \\ 0 & \text{in } \Omega_B \end{cases}$$

$$\partial_t h + g_{\text{ion}}(v_m, h) = 0 \quad \text{in } \Omega_M$$

With the CEM transmission conditions

$$j_i = -\sigma \nabla u \cdot n_i = c_i \partial_t (U_i - u|_{\Gamma_i}) + \frac{1}{r_i} (U_i - u|_{\Gamma_i}), \quad i \in \{\text{tip}, \text{ring}\}$$

Energy estimate

- There is an inequality if energy, which states the energy associated to each (equivalent) dipole in the overall electrical circuit

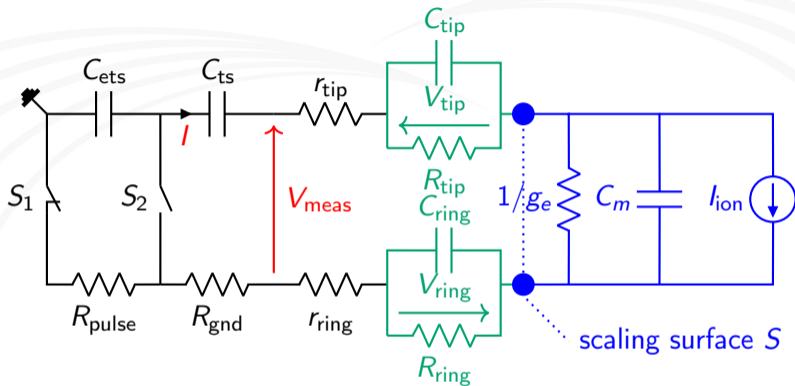
For test functions $w_i(x)$, $w(x) \in H^1$, and $W_{\text{tip}}, W_{\text{ring}} \in \mathbb{R}$,

$$\begin{aligned} & \int_{\Omega_M} \sigma_i \nabla u_i \cdot \nabla w_i + \int_{\Omega} \sigma \nabla u \cdot \nabla w + \int_{\Omega_M} (c_m \partial_t v_m + I_{\text{ion}}) w_m \\ & + \sum_{k \in \{\text{tip}, \text{ring}\}} \int_{\Gamma_k} \left(c_k \partial_t (U_k - u|_{\Gamma_k}) + \frac{1}{r_k} (U_k - u|_{\Gamma_k}) \right) (W_i - w|_{\Gamma_i}) \\ & + C \frac{dU_{\text{tip}}}{dt} W_{\text{tip}} + \frac{1}{R} U_{\text{ring}} W_{\text{ring}} = 0 \end{aligned}$$

- \rightarrow adapt the standard⁴ existence proof (article in preparation), and error estimate for FEM

⁴Bourgault, Coudière, and Pierre, “Existence and uniqueness of the solution for the bidomain model used in cardiac electrophysiology”.

A surrogate 0D model



We need to rescale the current per unit of surface (ionic) to a current:

$$I = S \left(C_m \frac{dV_m}{dt} + I_{ion} + g_e V_m \right)$$

Surrogate 0D model ODEs

$$\frac{dl}{dt} + \frac{1}{\tau} l = \frac{1}{R_{\text{tot}}} \left(\frac{V_{\text{tip}}}{\tau_{\text{tip}}} + \frac{V_{\text{ring}}}{\tau_{\text{ring}}} + \frac{l_{\text{ion}}(V_m, h)}{C_m} + \frac{V_m}{\tau_m} \right) \quad (1)$$

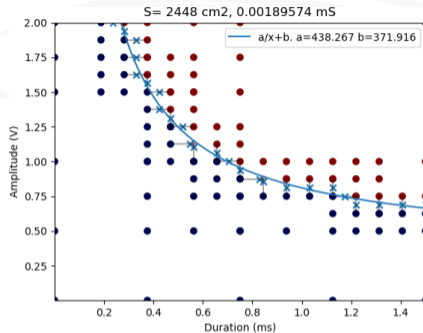
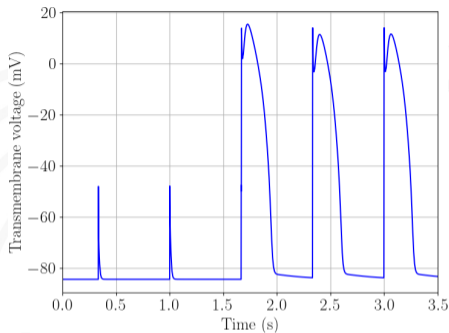
$$\frac{dV_i}{dt} + \frac{V_i}{\tau_i} = \frac{l}{C_i}, \quad i \in \{\text{tip}, \text{ring}\} \quad (2)$$

$$\frac{dV_m}{dt} + \frac{l_{\text{ion}}(V_m, h)}{C_m} + \frac{V_m}{\tau_m} = \frac{l}{SC_m}, \quad (3)$$

$$\frac{dh}{dt} + g(V_m, h) = 0, \quad (4)$$

- How to choose S and g_e ?
- Our starting choice: $S = 100\text{cm}^2$ and $g_e = 10^{-2}\text{mS}$, obtained from a volume of 1mm^3

Threshold detection in the model



- Capture := more than 50% successful captures, seen on V_m
- a 2D dichotomy algorithm \rightarrow intervals $(V_{\min}(T), V_{\max}(T))$
- *Rheobase* V_\star (0.372 V) and *chronaxie* T_\star (1.18 ms) from the Lapicque law (LS fitting):

$$V_{\text{Lapicque}}(T) := V_\star \left(1 + \frac{T_\star}{T} \right), \quad \text{an minimize} \quad \left| V_{\text{Lapicque}}(t) - \frac{1}{2} (V_{\min}(t) + V_{\max}(t)) \right|_{\ell^2}^2$$

First comparisons – experiments and 0D model, see⁵

- Beeler-Reuter ionic model, with parameters from CellML
- Contact parameters fixed from the bath experiments

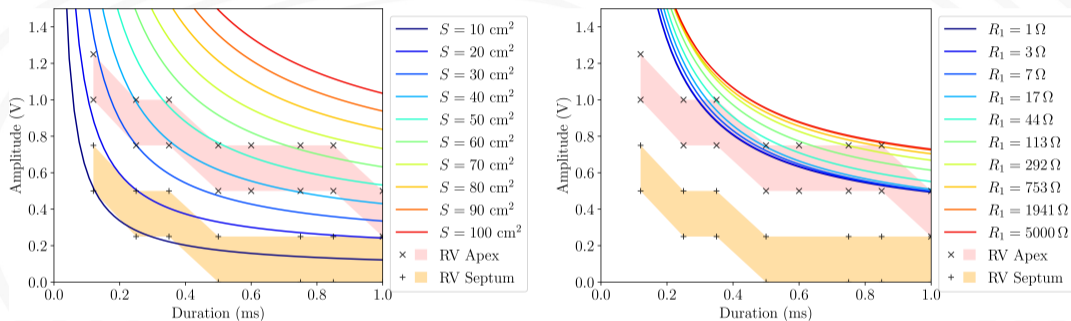


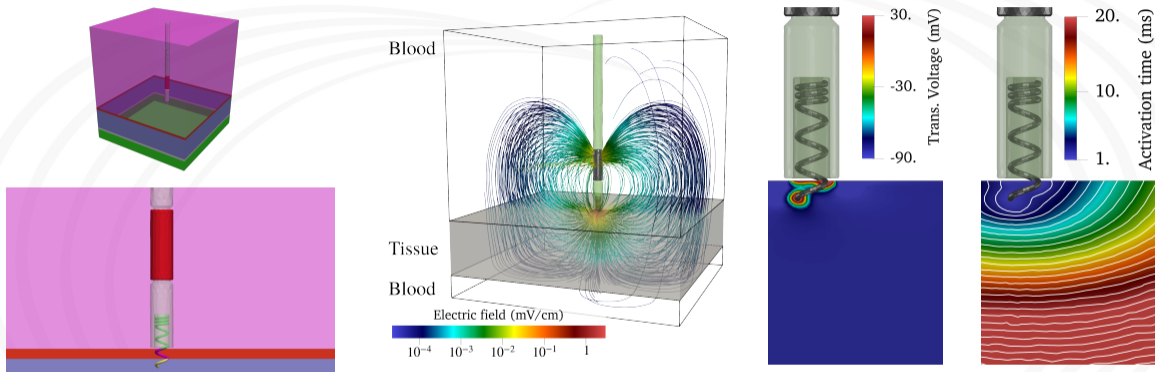
Figure: Comparison of Lapique curves (solid lines) computed with different values of S (left) and R_{tip} (right). The shaded regions indicate where the experimental capture threshold is located.

⁵Pannetier, Leguèbe, Coudière, Walton, Feuerstein, and Amaro, “Modeling cardiac stimulation by a pacemaker, with accurate tissue-electrode interface”.

Remarks

- Pacemakers have very sparse covering of the Lopicque plane, but we model the pacemaker
 $T \in \{0.12, 0.25, 0.35, 0.5, 0.75, 0.85, 1.00\} \text{ms}$, $V \in \{2.0, 1.75, 1.5, 1.0, 0.75, 0.5, 0.25\} V$
- Lopicque law fits well the model
- Lopicque law do not fit within the experimental regions
- (Too ?) many modeling simplification ?
 - ▶ 0D – 1 cell
 - ▶ g_e and S : influence of $g_e \ll$ influence of S
 - ▶ Contact properties in bath *versus* tissue ? Influence of R_{tip}
 - ▶ BR model with CellML std parameters
- What about the V&V40 guidelines
- Fast computations, OK for prototyping ideas / computational procedures

Some preliminary 3D results I

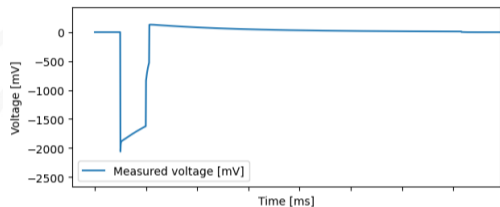


Mesh resolution $6\mu\text{m} - 1.5\text{mm}$, time-step $10\mu\text{s}$, P1-Lagrange FEM, BDF2+RL2, BiCGStab

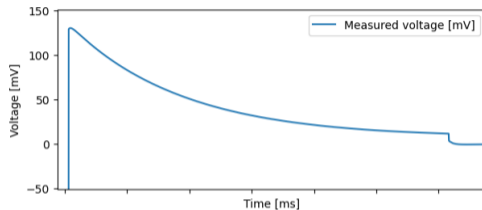
Supra-threshold pacing, $T = 1\text{ms}$ and $V = 2.5\text{V}$

Standard CellML BR model + electrical conductivity coefficients

Some preliminary 3D results II



(a) Simulated voltage V_{meas} , capture case



(b) voltage during OCD, capture case

Figure: We obtain the expected behavior for V_{meas}

The V&V40 framework

Next: how to make it useful and credible ?

QoI: What is the energy level needed to capture a heart beat ?

CoU: As it would be reported by threshold detection procedures during animal experiments

Model influence	high	3	4	5
	medium	2 COU	3	4
	low	1	2	3
		low	medium	high
		Decision consequence		

Figure 2: Model Risk Matrix (cf. ASME VV40) evaluating the COU included in UCI.

(a) Risk matrix foll. ASME VV40



(b) V: 231 pages



(c) V: 151 pages

Work on verification

Table 6: Verification Credibility Factors Coverage Level for Use Case 1 (cf. ASME VV40); * indicates verification activities not yet completed.

		Model Risk				
		x				
Credibility Factor Coverage Level		1	2	3	4	5
Code Verification: Software Quality Assurance	V		x			
Code Verification: Numerical Code Verification - NCV	V		x			
Calculation Verification - Discretization Error *	V		x			
Calculation Verification - Numerical Solver Error *	V		x			
Calculation Verification - Use Error	IV		x			

SQA: software code CEPS, thorough CI, SonarQube analysis, ...

NCV, discretization error, solver error: that is numerical analysis.

We provide many automatic tests (interpolation, quadrature, ODE solvers) and convergence tests on PDEs (Laplace, heat, reaction-diffusion) w/r to manufactured and reference solutions

Use error: on the web-based platform + within SQA

We cover credibility up to 4 or 5, while 2 is needed (risk analysis).

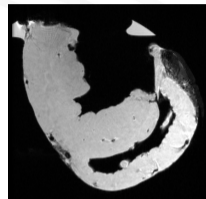
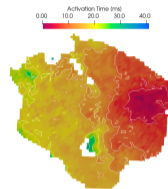
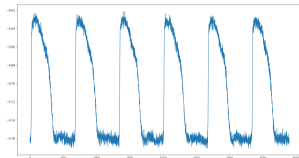
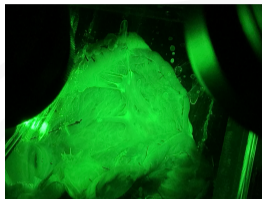
On-going work on validation

Table 6 : Validation and Applicability Credibility Factors Coverage Level for Use Case 1 (cf. ASME VV40);
 * indicates validation activities not yet completed; N/A indicates activities which requires completion to be evaluated.

		Model Risk				
		Credibility Factor Coverage Level				
		1	2	3	4	5
Validation - Model [Form]	III	x				
Validation - Model [Inputs] *	III	x				
Validation - Comparator [Test Samples] *	IV	x				
Validation - Comparator [Test Conditions] *	II	x				
Validation - Assessment [Input Parameters] *	III	x				
Validation - Assessment [Output Comparison]	N.A.	x				
Applicability: Relevance of the Quantities of Interest *	V	x				
Applicability: Relevance of the Validation Activities to the COU *	V	x				

- To be done in view of the QoI and CoU
- For UC1 (Simcardiotest), we could design and run our own experiments

Path to calibration, before validation



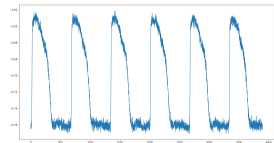
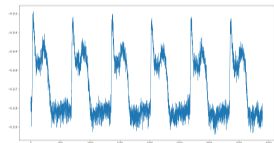
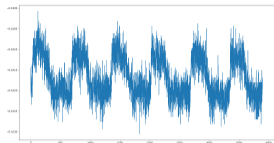
Calibrate model's parameters

- Contact parameters → done (bath experiments)
- Ionic parameters → optical signal, pixel-wise, done
- Conductivity coefficients → 9.4T MRI (300 μm) + activation maps, partially done

Compare to experiments for validation

- Lapicque curves are within the experiment Lapicque regions? Computational challenge

Ionic parameters for the BR model



- BR has 2 parameters for the Na^+ current: g_{Na} and $g_{\text{Na},c}$
- Optimisation technique developed in^a: compass search algorithm
- Automatic search in each pixel of each camera (2 camera)
- Using 6 consecutive pacings, beginning of the experiment
- Data has to be normalized (either baseline only or baseline + peak)

^aPongui Ngoma, Bourgault, Pop, and Nkounkou, "Adjustment of Parameters in Ionic Models Using Optimal Control Problems".

Identification of parameters for 1 pixel

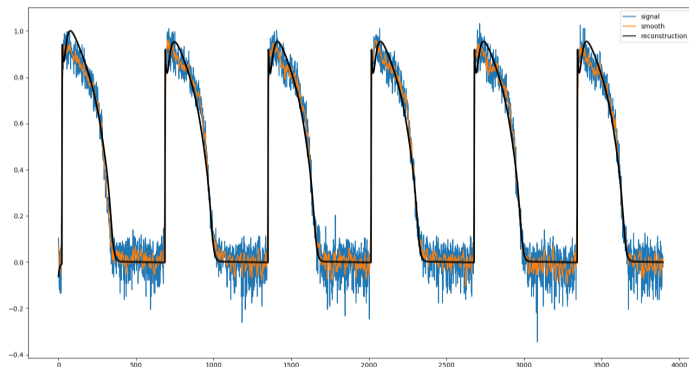


Figure: Exemple identification match. Raw signal (blue), filtered one (orange), and model (black).

Spatial distribution of g_{Na} and $g_{Na,c}$

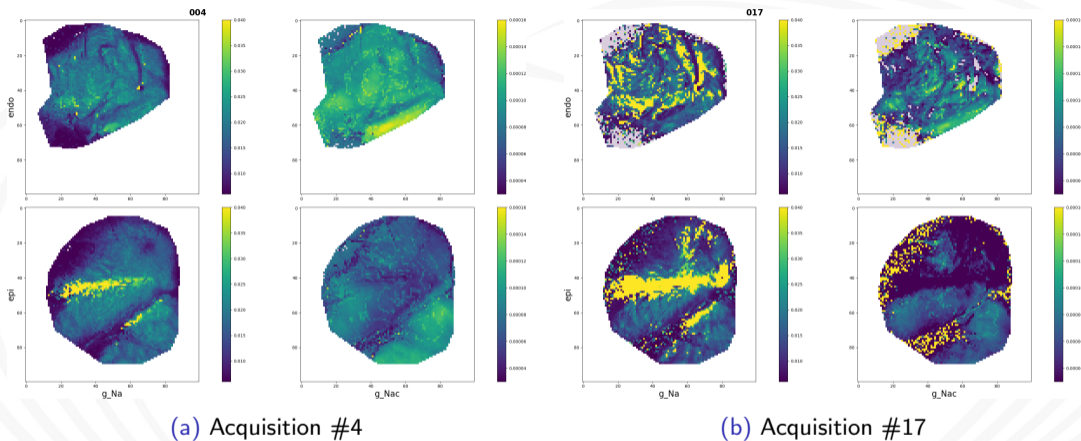


Figure: g_{Na} (left) and $g_{Na,c}$ (right) on endo (top) and epi (bottom) – 2 acquisitions.

Endo / epi distribution of parameters

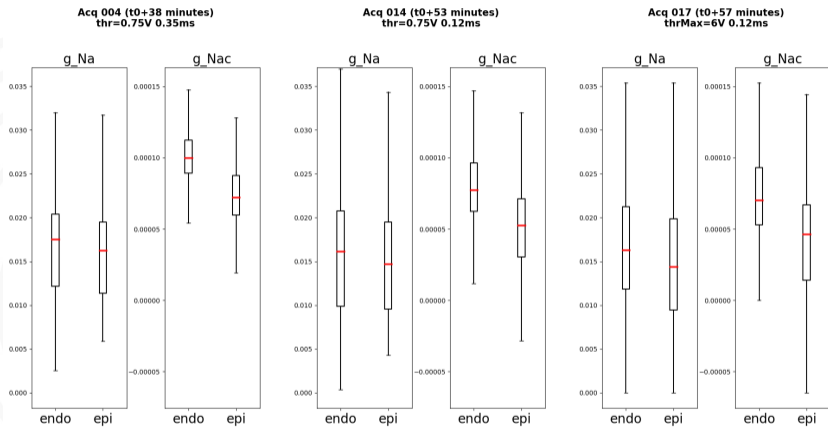
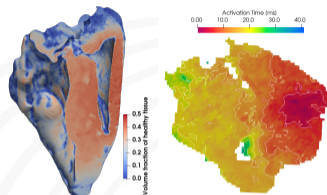


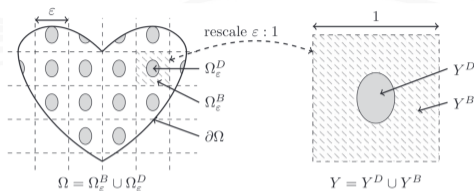
Figure: Statistical distribution of identified g_{Na} and $g_{Na,c}$

Microstructure around the tip : conductivity coefficients

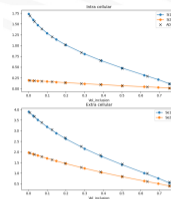


(a) volume fraction

(b) optical map window



(c) homogenization principle⁶



(d) conductivity coefficients

- Segmentation and fiber direction → done (thanks to V. Ozenne, J. Magat)
- Volume fraction → done⁷
- How to register the optical window to the the MR image (folded sample) ?

⁶Davidović, Coudière, and Bourgault, “Modelling the action potential propagation in a heart with structural heterogeneities: From high-resolution MRI to numerical simulations”.

⁷Ibid.

Conclusion

- Bridging between bioimpedance (signal processing) and bidomain (PDE modeling)
- The computational pipeline is complete
- The software did undergo a thorough verification process
- Validation experiment were specifically designed, that is on-going work
- It remains possible improvements (numerics) to study
- Overall, the V&V process was certainly helpful



Thanks for your attention!

Other references I



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