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Numerical simulation of cardiac pacing devices: modeling and validation issues

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IMB – UMR 5251, Liryc, Inria Carmen – Université de Bordeaux – CNRS – Bordeaux-INP

November 16, 2023



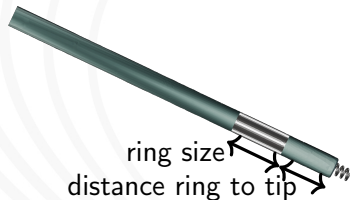
**SIM
CARDIO
TEST**

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

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 ?

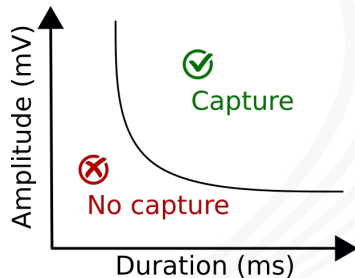
Context: threshold test in animal experiments. Influence of the design of the lead, like geometry and contact properties ?



Computer model
and simulation

Verification and
validation

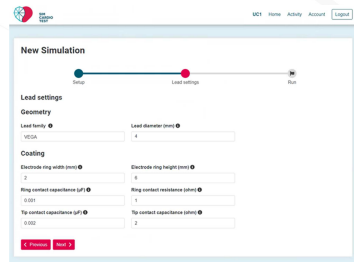
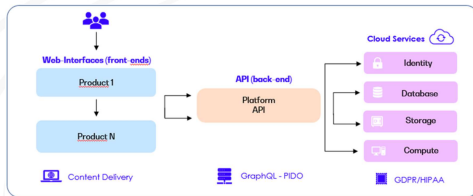
Input: design parameters



Output: Lapicque curve

Web-based computational platform

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



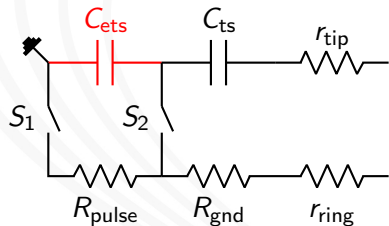
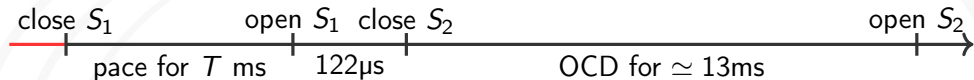
 InSilicoTrials

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): $\simeq 13\text{ms}$



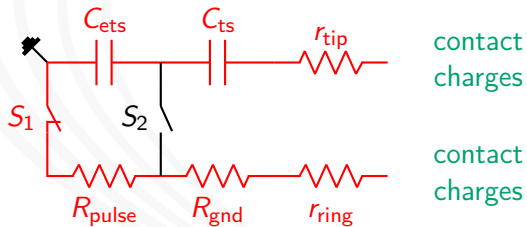
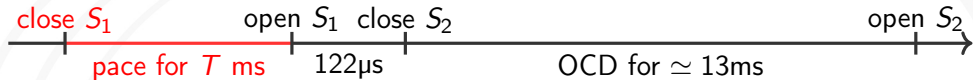
contact
?

contact
?

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

Time course of an electrical pulse

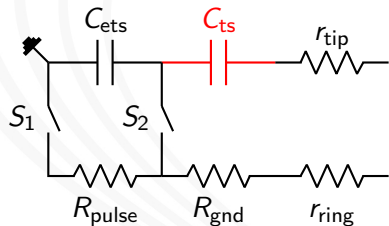
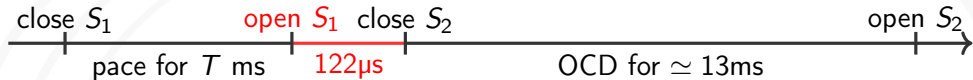
- 1 **Pacing:** for duration T (ms), with charge Q (eq. V)
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electrolytic bath \rightarrow bench exp.
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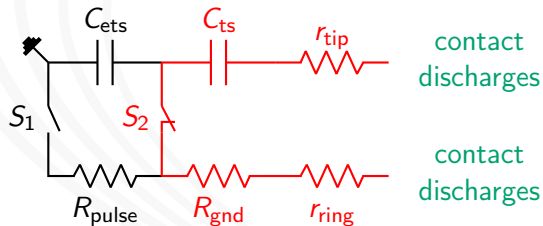
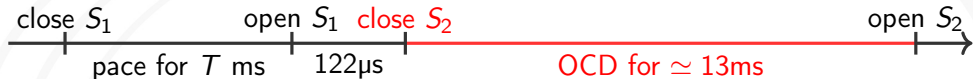
contact
discharges

contact
discharges

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

Time course of an electrical pulse

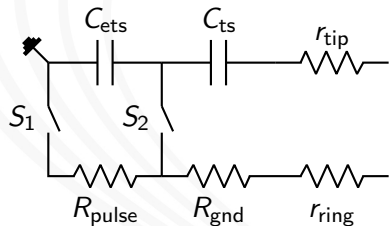
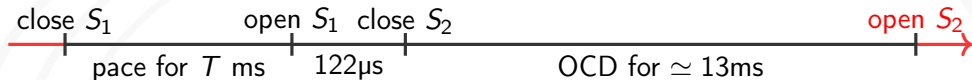
- 1 Pacing: for duration T (ms), with charge Q (eq. V)
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- 3 **Output Capacitor Discharge (OCD): $\simeq 13\text{ms}$**



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

Time course of an electrical pulse

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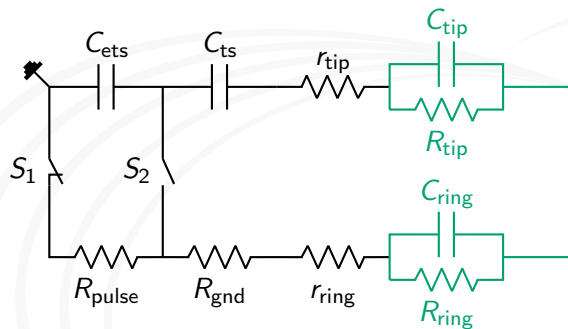


contact
?

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

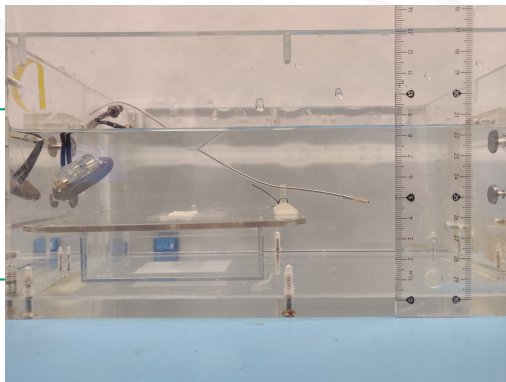
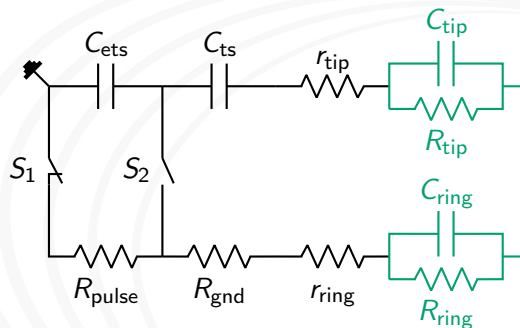
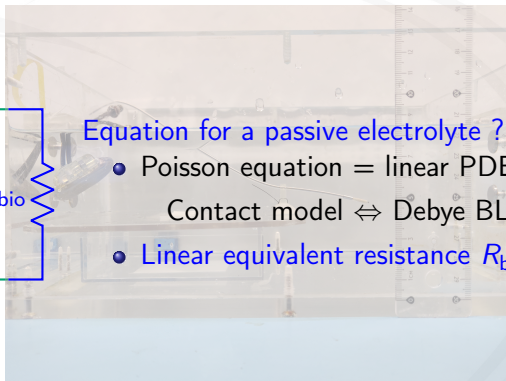
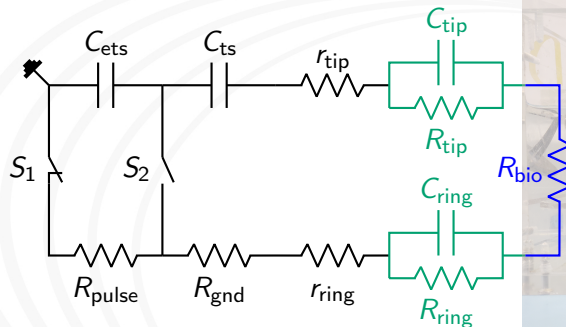


Figure: Passive bath \rightarrow def of contact model and parameter identification

Bath experiment / model

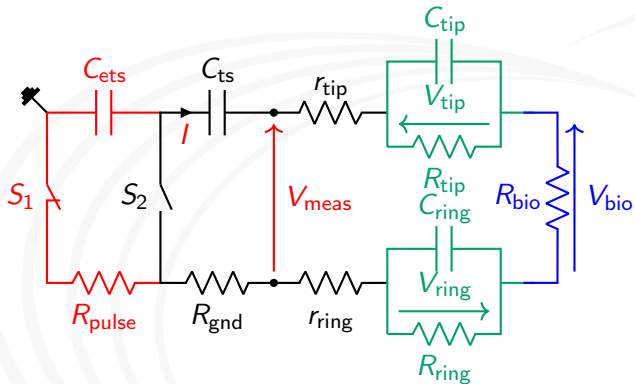


Equation for a passive electrolyte ?

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

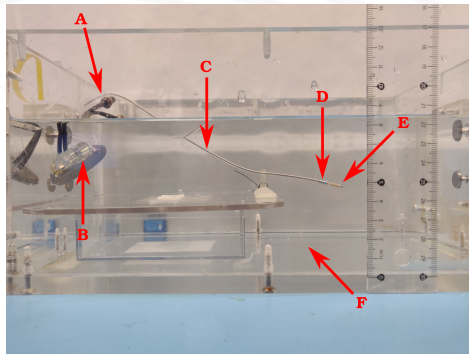
Figure: Passive bath \rightarrow def of contact model and parameter identification

The passive bath model



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

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

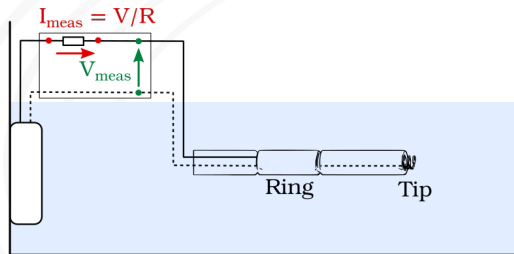


$$\frac{dl}{dt} + \frac{1}{\tau} l = \frac{1}{R_{\text{tot}}} \left(\frac{V_{\text{tip}}}{\tau_{\text{tip}}} + \frac{V_{\text{ring}}}{\tau_{\text{ring}}} \right)$$

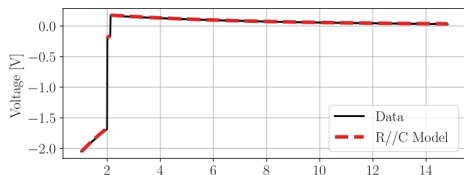
$$\frac{dV_i}{dt} + \frac{V_i}{\tau_i} = \frac{I}{C_i}, \quad i \in \{\text{tip}, \text{ring}\}$$

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

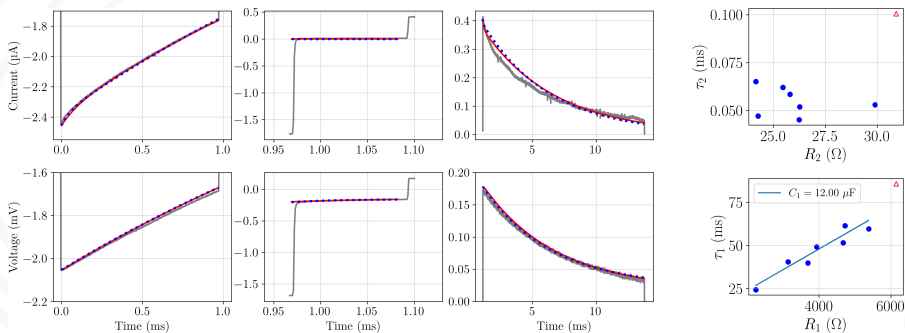


Figure: Current and voltage in each step, measures and model (left), and parameters (right)

Tissue experiment / model

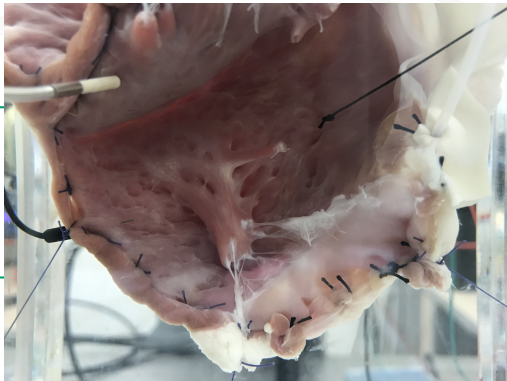
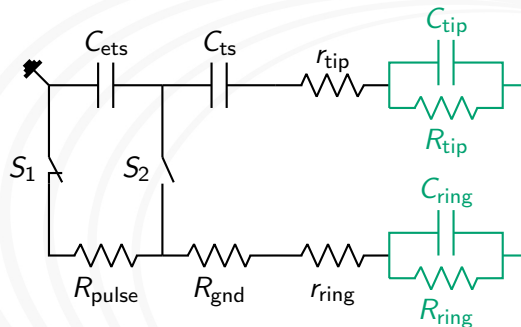
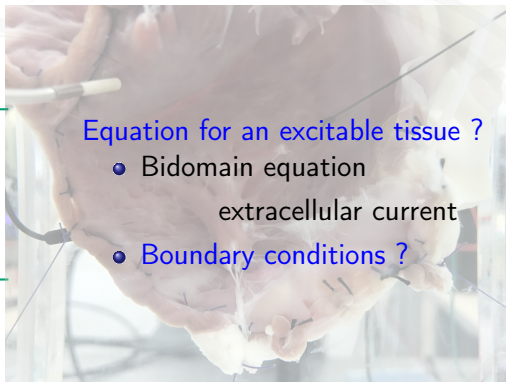
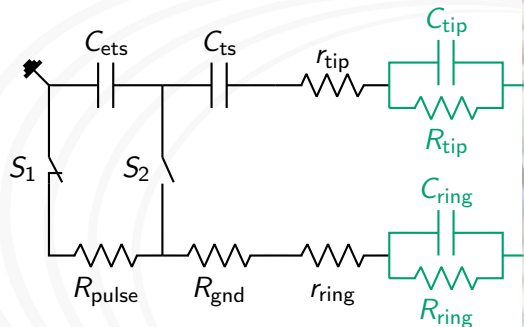


Figure: Animal experiment \rightarrow validation data

Tissue experiment / model

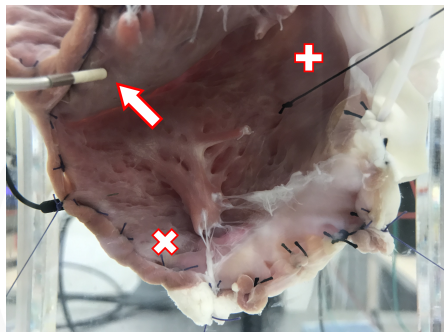


Equation for an excitable tissue ?

- Bidomain equation
extracellular current
- Boundary conditions ?

Figure: Animal experiment → validation data

Threshold detection tests in animal experiments

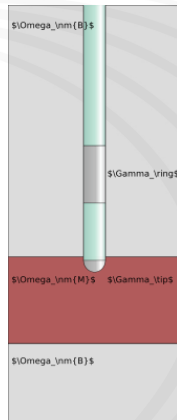
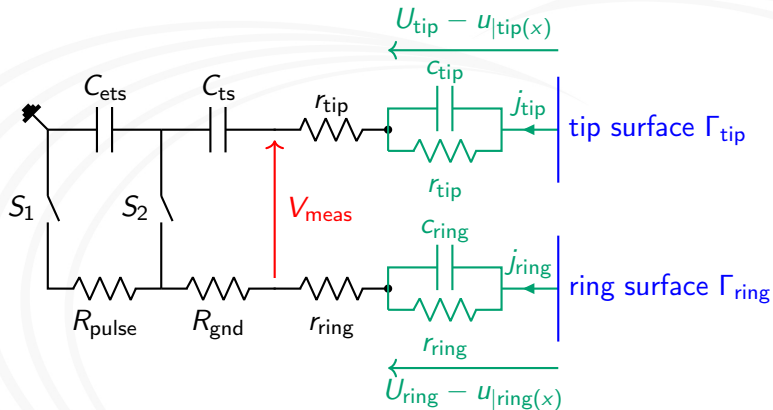


- Ventricular wedge preparation, 2 sheeps (now 3)
- 3 sites: apex (X), septum (\rightarrow), base (+)
- screw fully deployed, perpendicular
- Recording of V_{meas}^* , like in the bath
- Recording of distant EGMs with needle electrodes
- Optical signals + 9.4T MRI

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

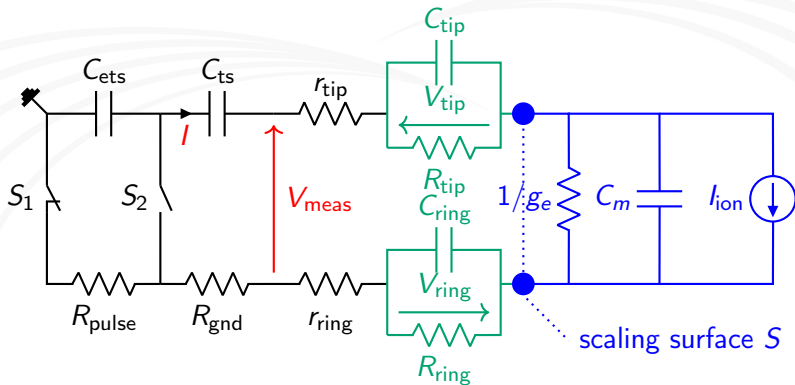
For test functions $w_i(x)$, $w(x) \in H^1$, and $W_{\text{tip}}, W_{\text{ring}} \in \mathbb{R}$,

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

- \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:

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

Surrogate 0D model ODEs

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

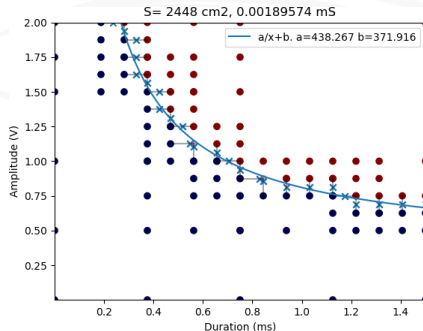
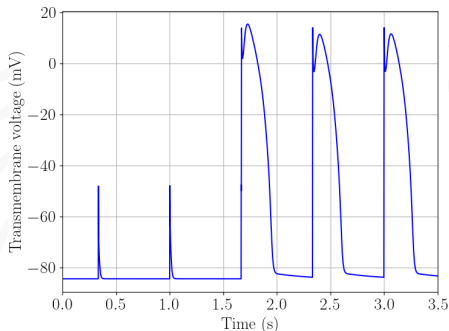
$$\frac{dV_i}{dt} + \frac{V_i}{\tau_i} = \frac{l}{C_i}, \quad i \in \{\text{tip}, \text{ring}\} \quad (2)$$

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

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

- 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

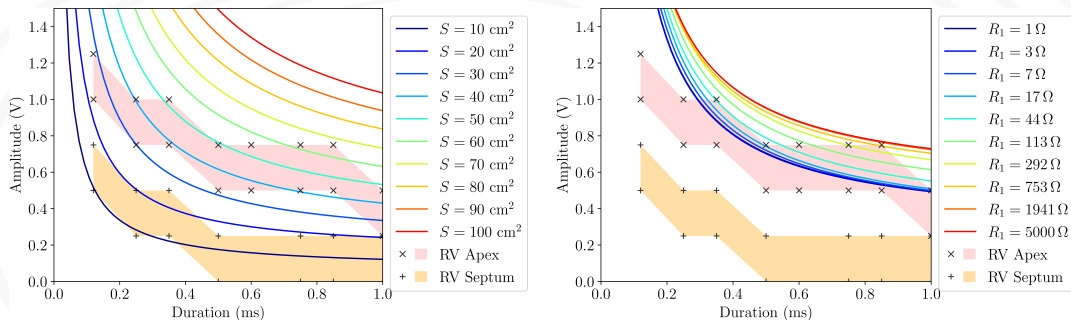


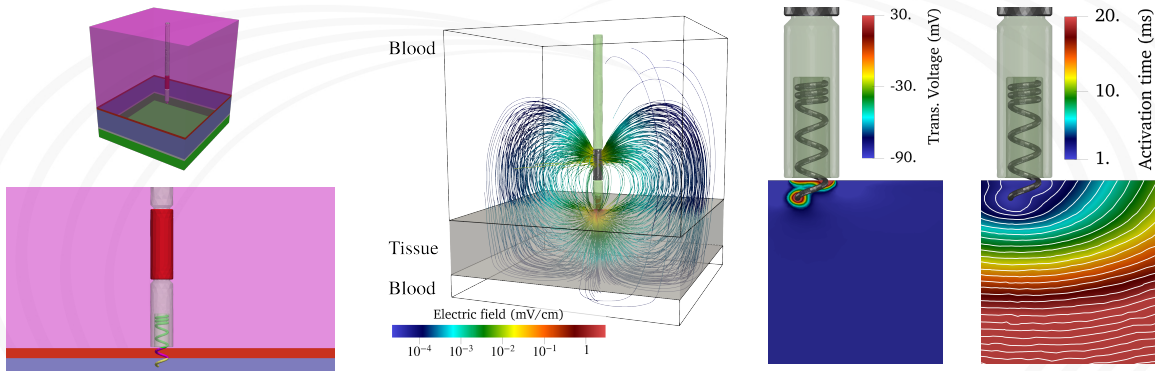
Figure: Comparison of Lapique curves (solid lines) computed with different values of S (left) and R_{tip} (right). The shaded regions indicate where the experimental capture threshold is located.

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

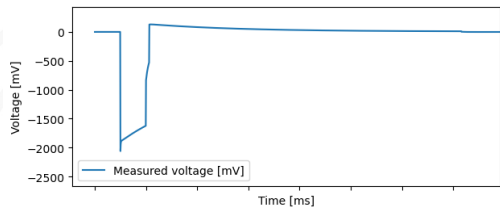


Mesh resolution $6\mu\text{m} - 1.5\text{mm}$, time-step $10\mu\text{s}$, P1-Lagrange FEM, BDF2+RL2, BiCGStab

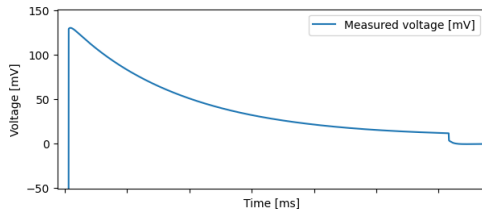
Supra-threshold pacing, $T = 1\text{ms}$ and $V = 2.5\text{V}$

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).

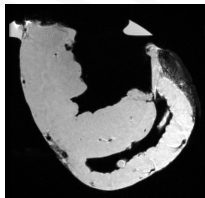
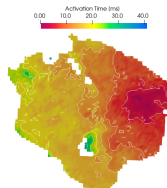
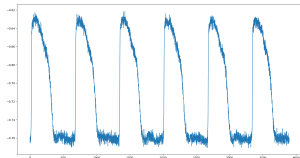
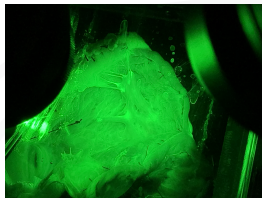
On-going work on validation

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



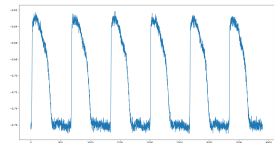
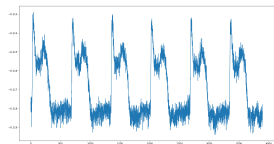
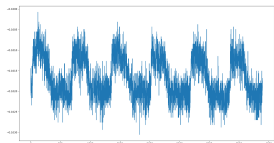
Calibrate model's parameters

- 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

- Lapique curves are within the experiment Lapique 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

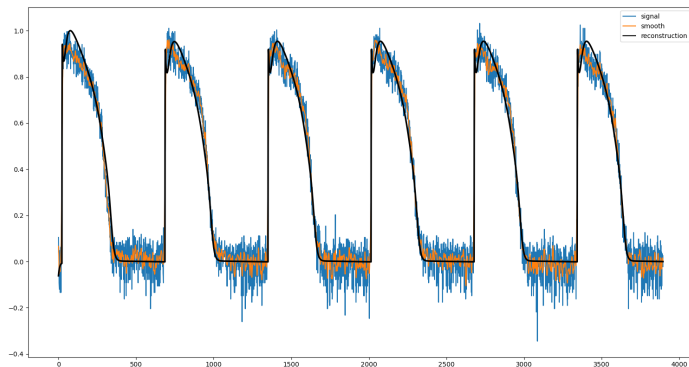
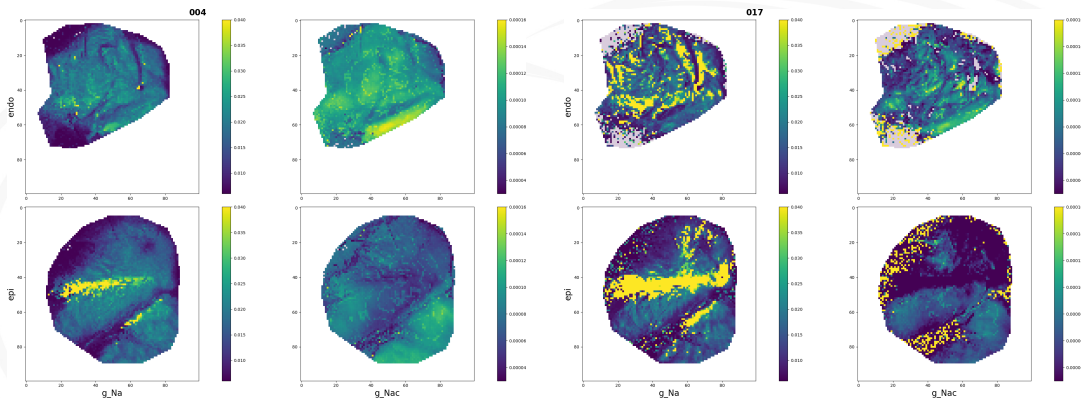


Figure: Exemple identification match. Raw signal (blue), filtered one (orange), and model (black).

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



(a) Acquisition #4

(b) Acquisition #17

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

Endo / epi distribution of parameters

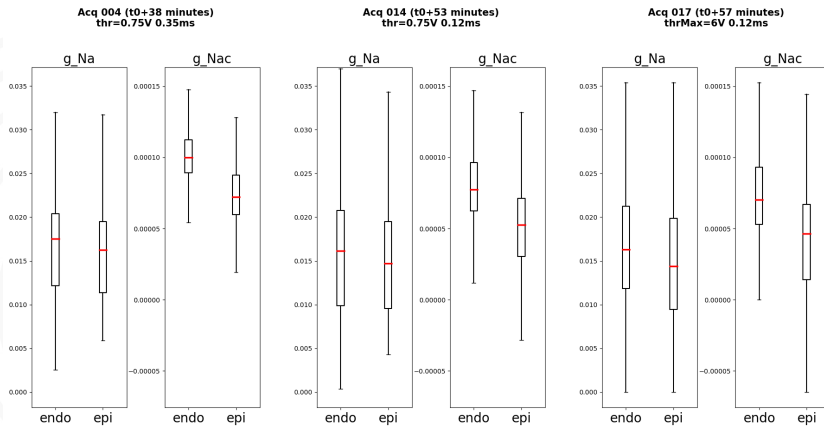
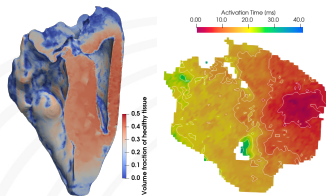


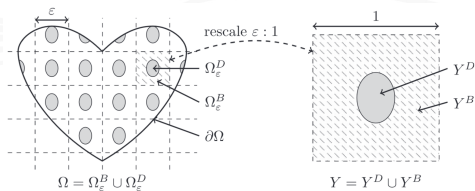
Figure: Statistical distribution of identified g_{Na} and $g_{Na,c}$

Microstructure around the tip : conductivity coefficients

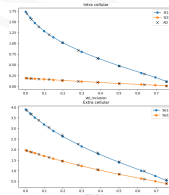


(a) volume fraction

(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



40-2018, ASME V&V. *Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices*. 2018.



Bourgault, Yves, Yves Coudière, and Charles Pierre. "Existence and uniqueness of the solution for the bidomain model used in cardiac electrophysiology". In: *Nonlinear Analysis: Real World Applications* 10.1 (Feb. 2009), pp. 458–482. DOI: 10.1016/j.nonrwa.2007.10.007.



Davidović, Anđela, Yves Coudière, and Yves Bourgault. "Modelling the action potential propagation in a heart with structural heterogeneities: From high-resolution MRI to numerical simulations". In: *International Journal for Numerical Methods in Biomedical Engineering* 37.11 (2021), e3322. DOI: 10.1002/cnm.3322.



Grimnes, Sverre and Ørjan G. Martinsen. *Bioimpedance and Bioelectricity Basics – Third Edition*. Elsevier, 2015. DOI: 10.1016/c2012-0-06951-7.



Pannetier, Valentin, Michael Leguèbe, Yves Coudière, Richard Walton, Delphine Feuerstein, and Diego Amaro. "Modeling cardiac stimulation by a pacemaker, with accurate tissue-electrode interface". In: *Functional Imaging and Modeling of the Heart*. Springer International Publishing, June 2023.



Pongui Ngoma, Diogène Vianney, Yves Bourgault, Mihaela Pop, and Hilaire Nkounkou. "Adjustment of Parameters in Ionic Models Using Optimal Control Problems". In: *Functional Imaging and modeling of the Heart*. Ed. by Mihaela Pop and Graham A. Wright. Vol. 10263. Lecture Notes in Computer Science. Springer, 2017, 322 ff.



Somersalo, Erkki, Margaret Cheney, and David Isaacson. "Existence and Uniqueness for Electrode Models for Electric Current Computed Tomography". In: *SIAM Journal on Applied Mathematics* 52.4 (1992), pp. 1023–1040. DOI: 10.1137/0152060. eprint: <https://doi.org/10.1137/0152060>.