Asymptotic Analysis of Electrocardiology Modeling after Pulsed Field Ablation

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Atrial Fibrillation

Context

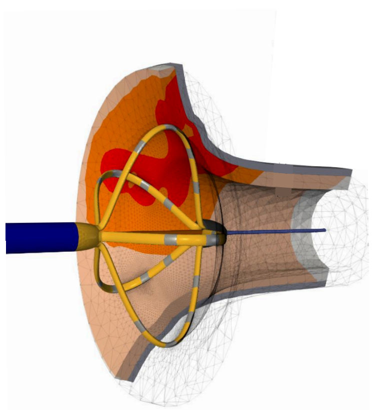
- One of the most important cardiac arrhythmias
- Chaotic electrical wave and irregular heartbeat
- Affects the pumping function of the heart

Treatment

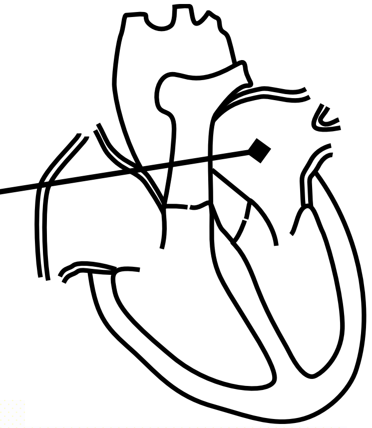
- Isolation of the 4 pulmonary veins

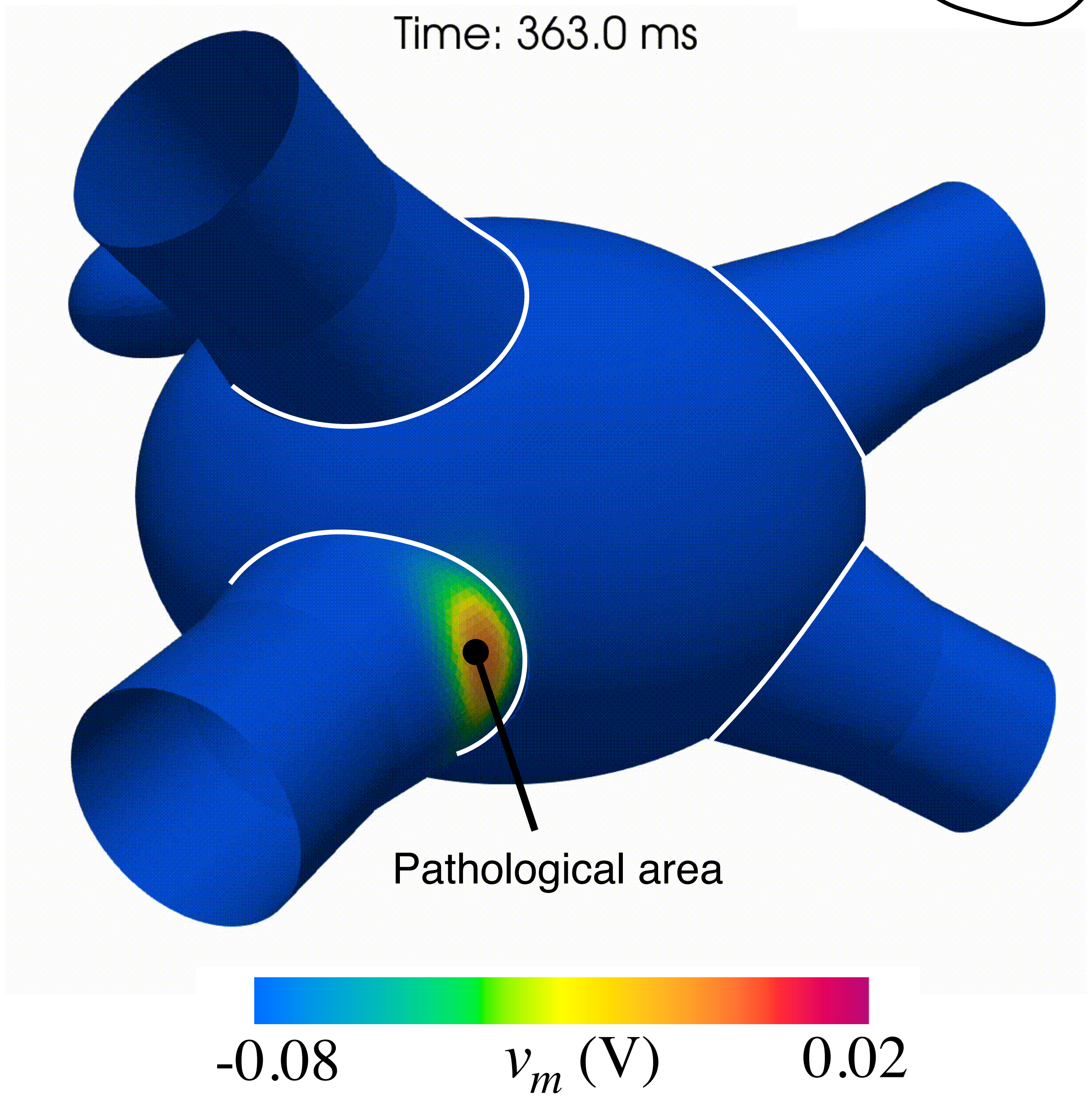
How

- Cardiac Ablation



Left Atrium





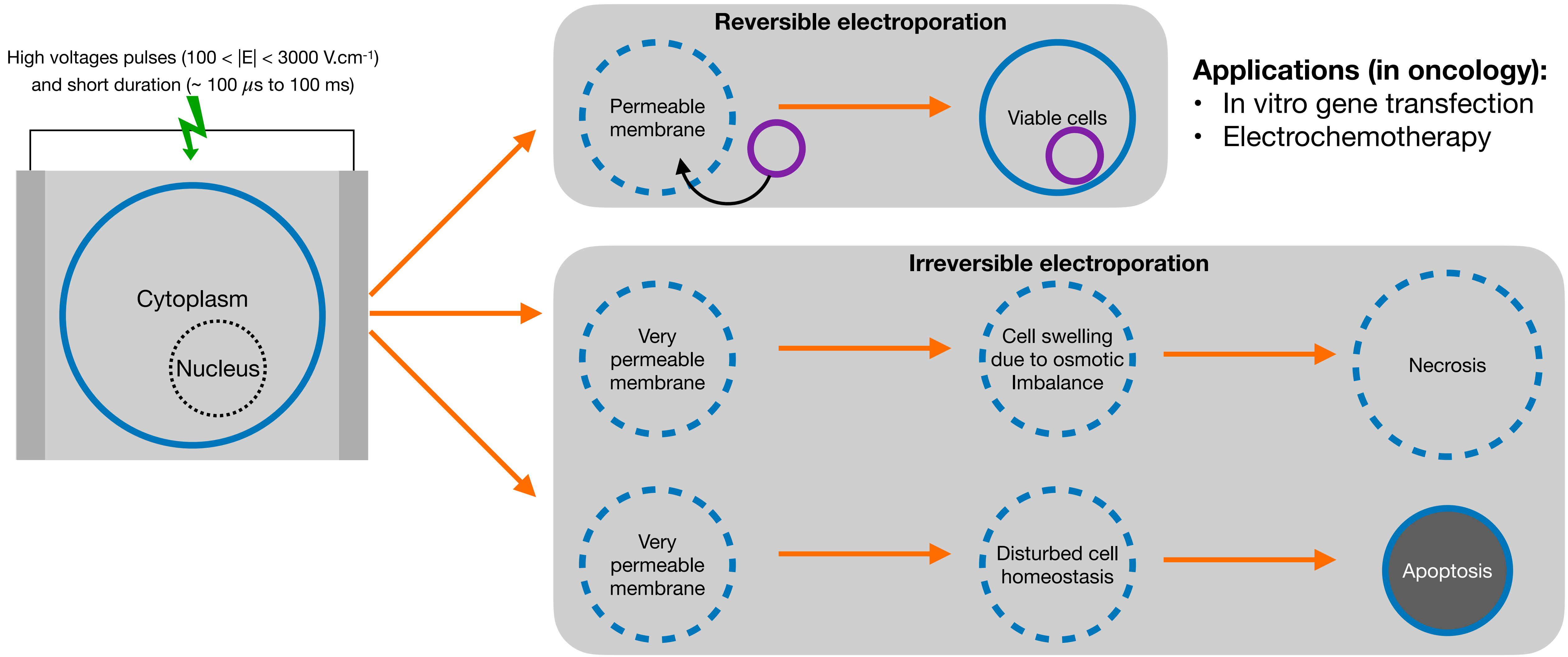
Cardiac Ablation

- Classical technique: **Radio-Frequency Ablation** (RFA).
  Clinics disadvantages [1]: damage to adjacent structures (lungs, phrenic nerve, oesophagus) and risk of "steam pop" mainly due to heat diffusion.
- Novel technique: **Pulsed Field Ablation** (PFA).
  Preservation of tissue scaffold, non thermal technique, which takes advantage of irreversible electroporation.

	RFA	**PFA**
Type of ablation	Thermal	Non-thermal
Tissue scaffold	Destruction	Preservation
Induced fibrosis	More	Few
Recurrency of AF	~ 30 %	~ 15%

[1] Wojtaszczyk A, Caluori G, Pešl M, et al. Irreversible electroporation ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2018; 29: 643–651.

Electroporation



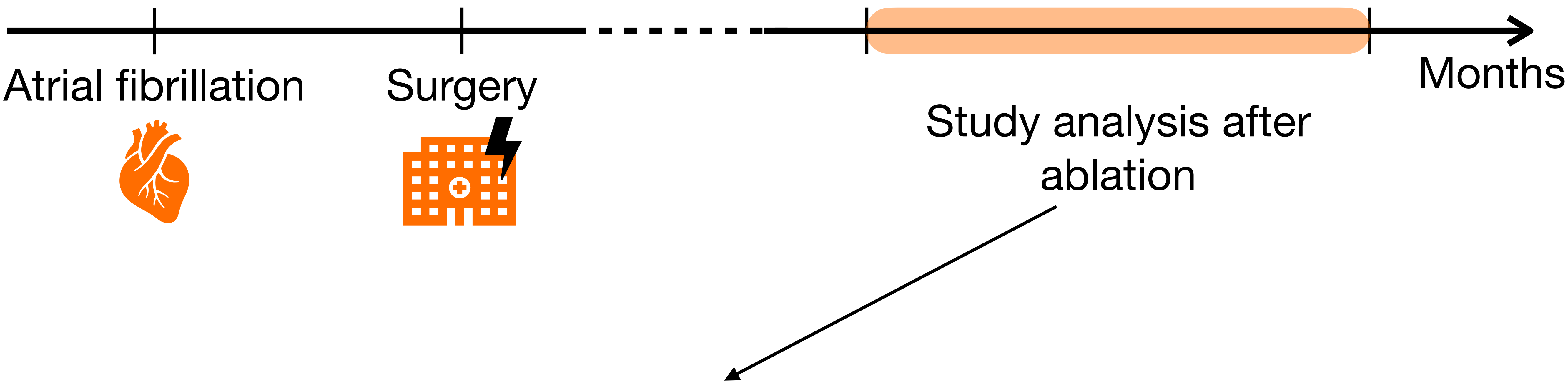
Applications (in oncology):

- In vitro gene transfection
- Electrochemotherapy

Application:

- Tumoral ablation
- Cardiac ablation

Goals



- 1st goal: model the behavior of electric potential in a cardiac tissue with an area ablated by PFA
- 2nd goal: compare models and simulations of PFA and RFA

Analysis after PFA

Modeling of electric potential

- Classic bidomain equations in Ω

$$
\begin{aligned}
A_m\left(C_m\frac{\partial v_m}{\partial t}+I_{ion}(v_m,w)\right)-\nabla\cdot(\bar{\bar{\sigma}}_i\cdot\nabla u_i)&=0, &&\text{in } \Omega\times(0,T)\\
A_m\left(C_m\frac{\partial v_m}{\partial t}+I_{ion}(v_m,w)\right)+\nabla\cdot(\bar{\bar{\sigma}}_e\cdot\nabla u_e)&=0, &&\text{in } \Omega\times(0,T)\\
\partial_t w+g(v_m,w)&=0, &&\text{in } \Omega\times(0,T)
\end{aligned}
$$

- Neumann BC + Gauge condition
- Scalar or tensor conductivities
- Intra-cellular potential u_i
- Extra-cellular potential u_e
- Transmembrane potential $v_m := u_i - u_e$
- Gating variable w

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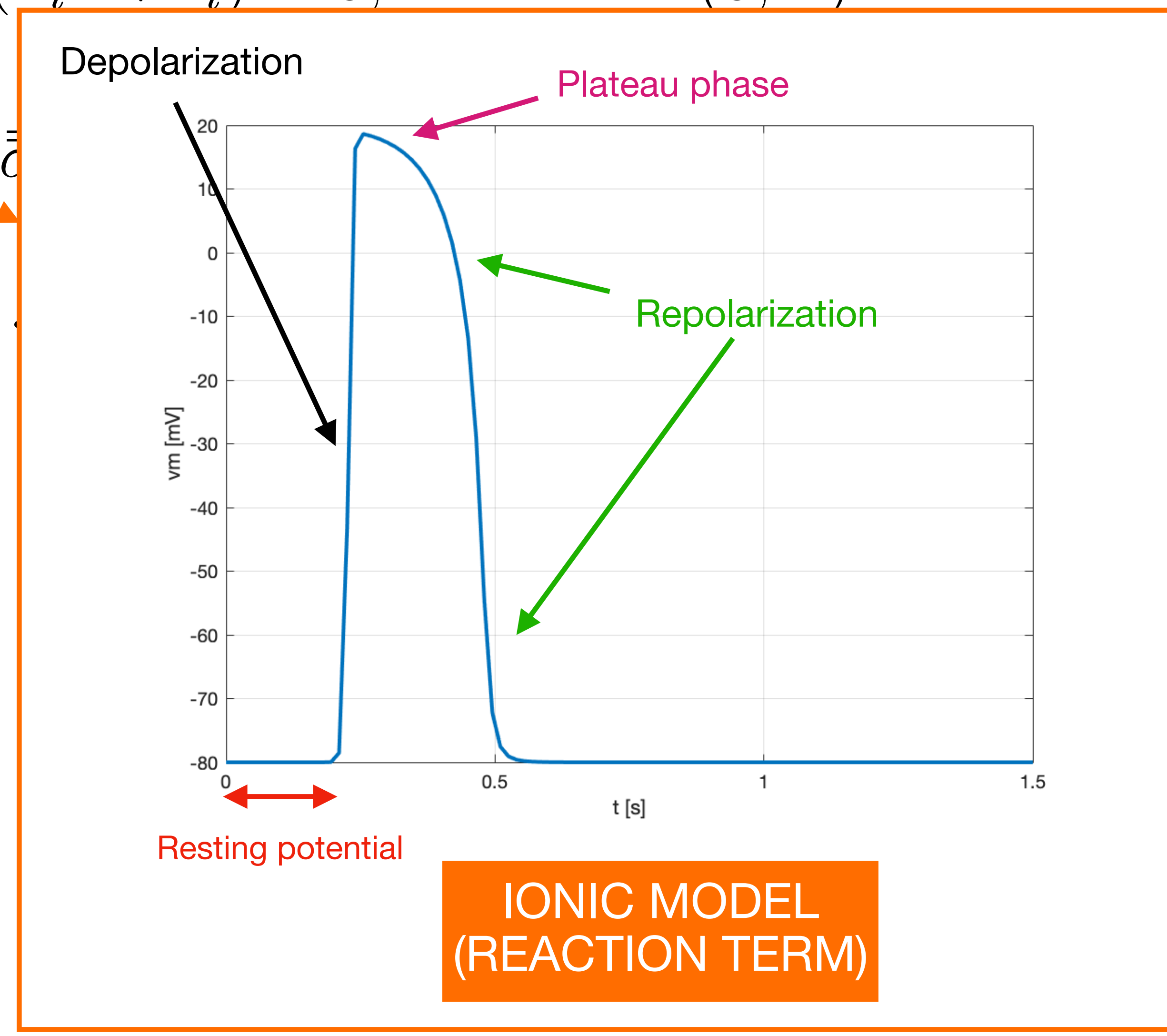
$$A_m\left(C_m\frac{\partial v_m}{\partial t}+I_{ion}(v_m,w)\right)-\nabla\cdot(\bar{\bar{\sigma}}_i\cdot\nabla u_i)=0,\qquad \text{in }\Omega\times(0,T)$$

$$A_m\left(C_m\frac{\partial v_m}{\partial t}+I_{ion}(v_m,w)\right)+\nabla\cdot(\bar{\bar{\sigma}}$$

$$\partial_t w+$$



- Neumann BC + Gauge condition
- Scalar or tensor conductivities
- Intra-cellular potential u_i
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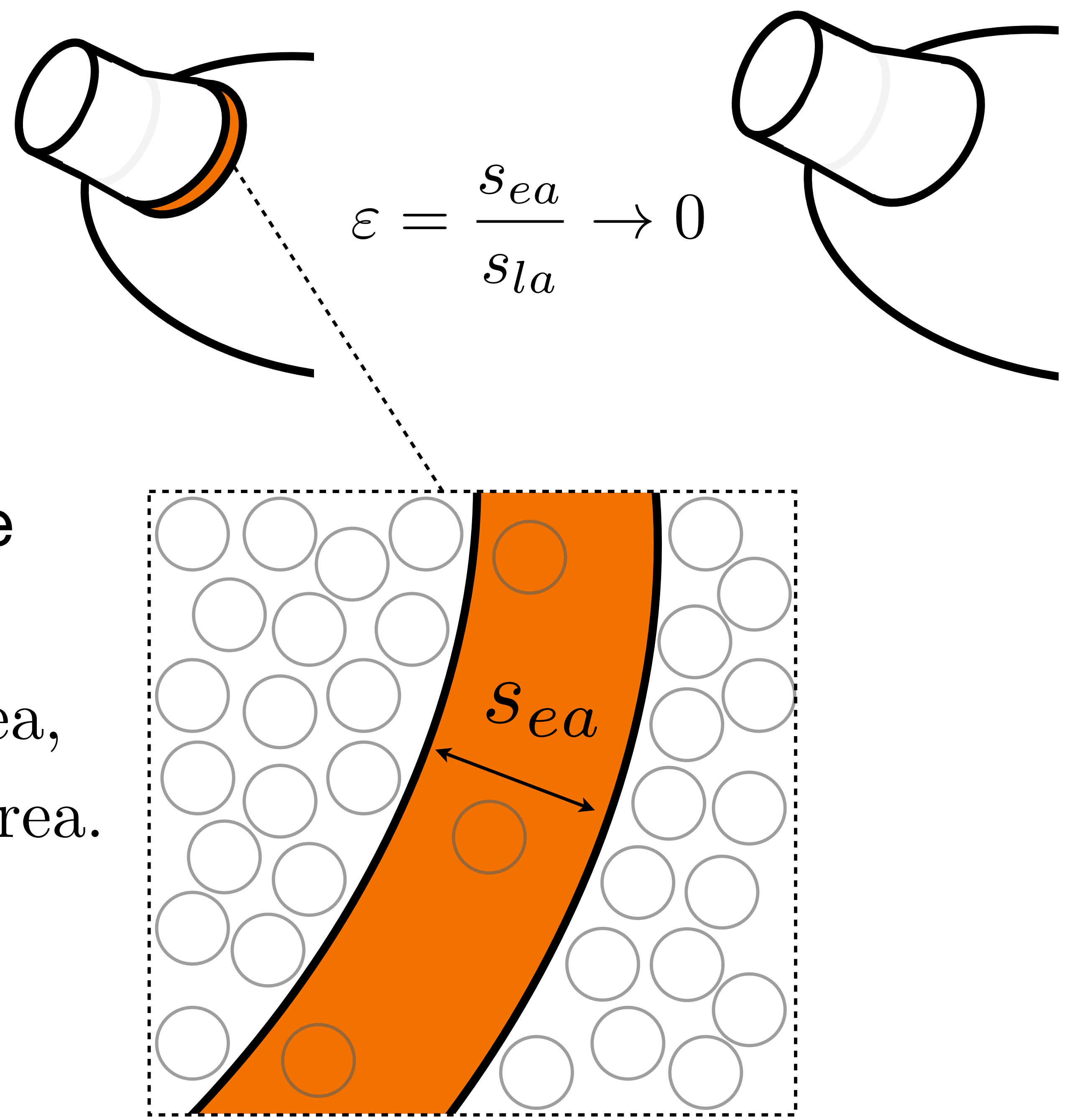
Analysis after PFA

Modeling the electroporated (EP) area



Assumptions

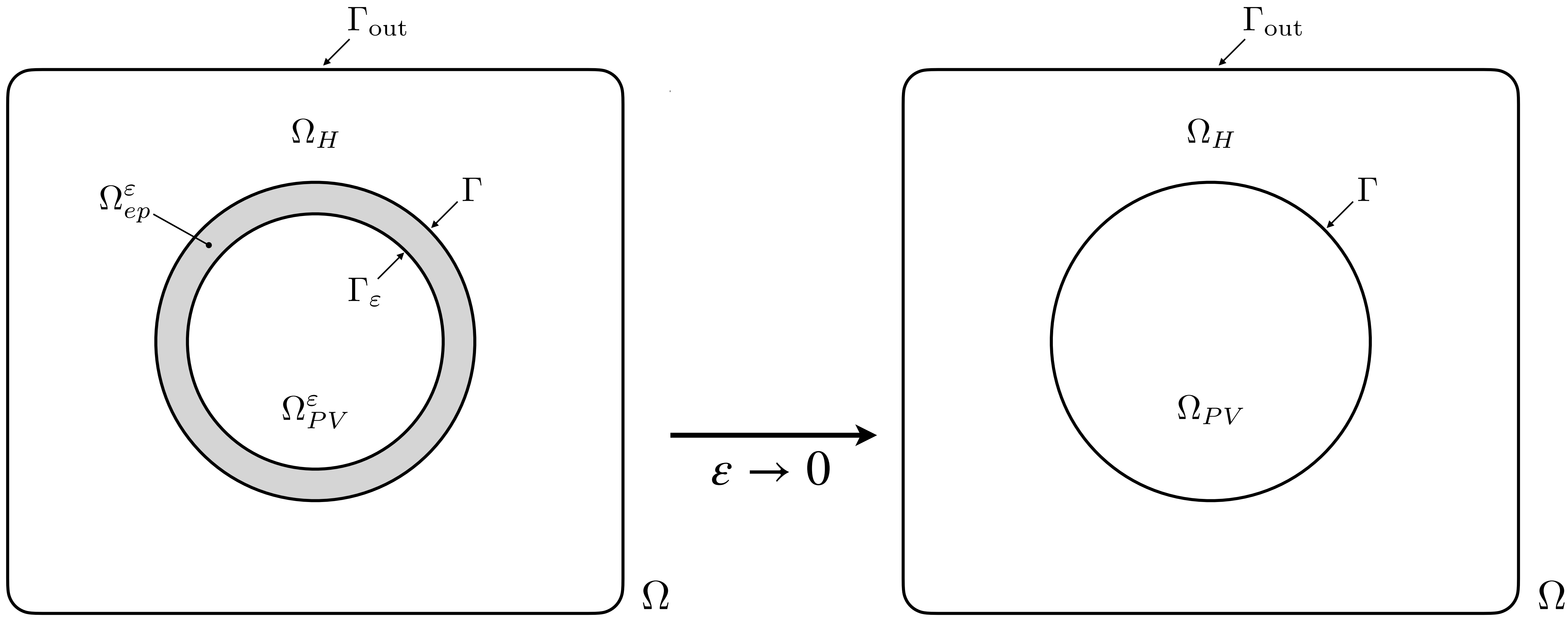
- The size of the EP area is considered thin.
- Almost all the cardiomyocytes are ablated by PFA : we assume

1. $$\bar{\bar{\sigma}}_i^{\varepsilon} = \begin{cases} \varepsilon^2 \bar{\bar{\sigma}}_i, & \text{inside EP area,} \\ \bar{\bar{\sigma}}_i, & \text{outside EP area.} \end{cases}$$

2. Linearization of the ionic current in the EP area.

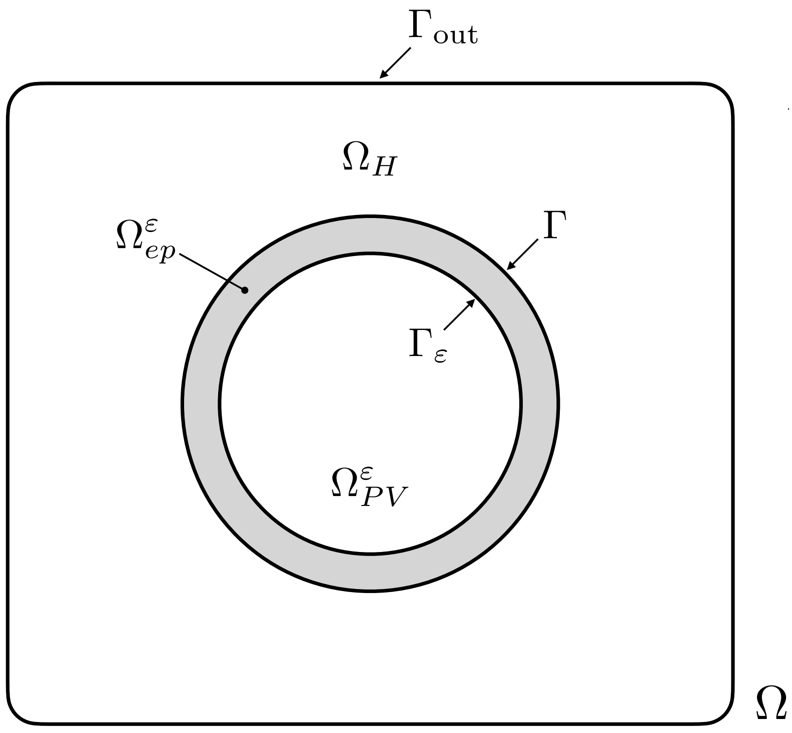
Analysis after PFA

Modeling the electroporated (EP) area



<u>Objective</u>
Determine transmission conditions at the interface Γ when $\varepsilon \to 0$.

Analysis after PFA



The static problem

$$
\begin{aligned}
-\nabla\cdot(\sigma_i\nabla u_i^\varepsilon) + A_m I_{ion}(u_i^\varepsilon - u_e^\varepsilon) &= \mathbb{1}_{\Omega_H} f, && \Omega_H \cup \Omega^\varepsilon_{PV},\\
-\nabla\cdot(\sigma_e\nabla u_e^\varepsilon) - A_m I_{ion}(u_i^\varepsilon - u_e^\varepsilon) &= -\mathbb{1}_{\Omega_H} f, && \Omega_H \cup \Omega^\varepsilon_{PV},\\
-\nabla\cdot(\varepsilon^2\sigma_i\nabla u_i^\varepsilon) + A_m S_0\,(u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega^\varepsilon_{ep},\\
-\nabla\cdot(\sigma_e\nabla u_e^\varepsilon) - A_m S_0\,(u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega^\varepsilon_{ep},
\end{aligned}
$$

coupled to transmission conditions,

$$
\begin{aligned}
[\![u_i^\varepsilon]\!]_\Gamma &= 0, & [\![\sigma_i^\varepsilon\partial_{\mathbf{n}} u_i^\varepsilon]\!]_\Gamma &= 0, & [\![u_e^\varepsilon]\!]_\Gamma &= 0, & [\![\sigma_e\partial_{\mathbf{n}} u_e^\varepsilon]\!]_\Gamma &= 0,\\
[\![u_i^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0, & [\![\sigma_i^\varepsilon\partial_{\mathbf{n}} u_i^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0, & [\![u_e^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0, & [\![\sigma_e\partial_{\mathbf{n}} u_e^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0,
\end{aligned}
$$

boundary conditions,

$$
\partial_{\mathbf{n}} u^\varepsilon_{i\,|\Gamma_{\text{out}}} = 0,\ \partial_{\mathbf{n}} u^\varepsilon_{e\,|\Gamma_{\text{out}}} = 0,
$$

and gauge condition

$$
\int_\Omega u_e^\varepsilon\,dx = 0.
$$

<u>First results</u>

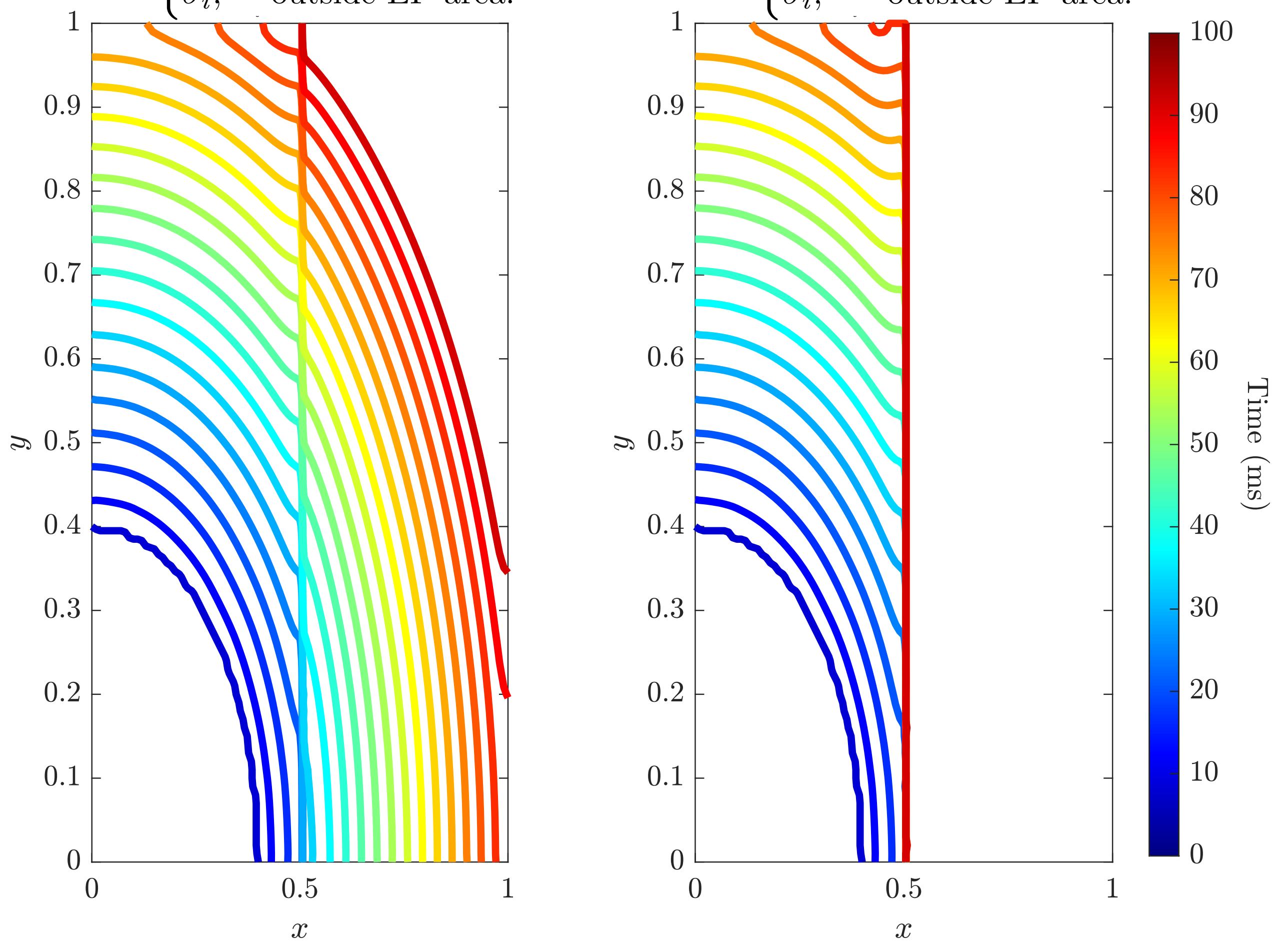
- **Existence and uniqueness**, under conditions on the ionic term.
- **A priori estimates**, allow the convergence.

Analysis after PFA

Why an asymptotic analysis?

$$
\begin{aligned}
-\nabla\cdot(\sigma_i\nabla u_i^\varepsilon) + A_m I_{ion}(u_i^\varepsilon - u_e^\varepsilon) &= \mathbb{1}_{\Omega_H} f, && \Omega_H \cup \Omega_{PV}^\varepsilon,\\
-\nabla\cdot(\sigma_e\nabla u_e^\varepsilon) - A_m I_{ion}(u_i^\varepsilon - u_e^\varepsilon) &= -\mathbb{1}_{\Omega_H} f, && \Omega_H \cup \Omega_{PV}^\varepsilon,\\
-\nabla\cdot(\varepsilon^2\sigma_i\nabla u_i^\varepsilon) + A_m S_0\,(u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega_{ep}^\varepsilon,\\
-\nabla\cdot(\sigma_e\nabla u_e^\varepsilon) - A_m S_0\,(u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega_{ep}^\varepsilon,
\end{aligned}
$$

$$\bar{\bar{\sigma}}_i^\varepsilon = \begin{cases} \varepsilon\bar{\bar{\sigma}}_i, & \text{inside EP area,}\\ \bar{\bar{\sigma}}_i, & \text{outside EP area.}\end{cases} \qquad \bar{\bar{\sigma}}_i^\varepsilon = \begin{cases} \varepsilon^2\bar{\bar{\sigma}}_i, & \text{inside EP area,}\\ \bar{\bar{\sigma}}_i, & \text{outside EP area.}\end{cases}$$



Solving the dynamic system with an adapted mesh…

Transmembrane potential v_m

Analysis after PFA

Why an asymptotic analysis?

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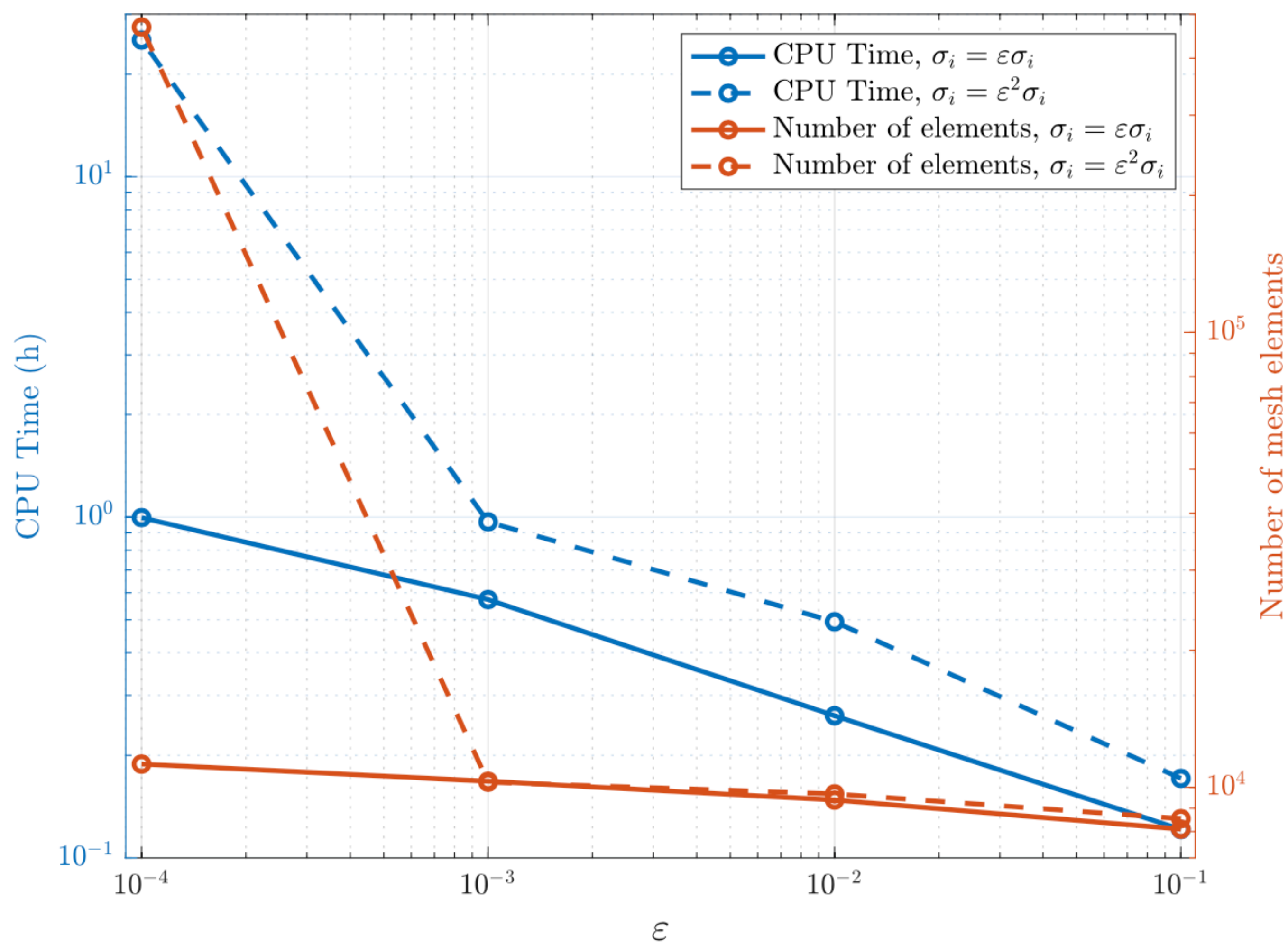
\begin{aligned}
-\nabla \cdot (\sigma_i \nabla u_i^\varepsilon) + A_m I_{ion}(u_i^\varepsilon - u_e^\varepsilon) &= \mathbb{1}_{\Omega_H} f, && \Omega_H \cup \Omega_{PV}^\varepsilon, \\
-\nabla \cdot (\sigma_e \nabla u_e^\varepsilon) - A_m I_{ion}(u_i^\varepsilon - u_e^\varepsilon) &= -\mathbb{1}_{\Omega_H} f, && \Omega_H \cup \Omega_{PV}^\varepsilon, \\
-\nabla \cdot (\varepsilon^2 \sigma_i \nabla u_i^\varepsilon) + A_m S_0\, (u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega_{ep}^\varepsilon, \\
-\nabla \cdot (\sigma_e \nabla u_e^\varepsilon) - A_m S_0\, (u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega_{ep}^\varepsilon,
\end{aligned}
$$

…numerical problems



Analysis after PFA

The asymptotic analysis

$$
\begin{aligned}
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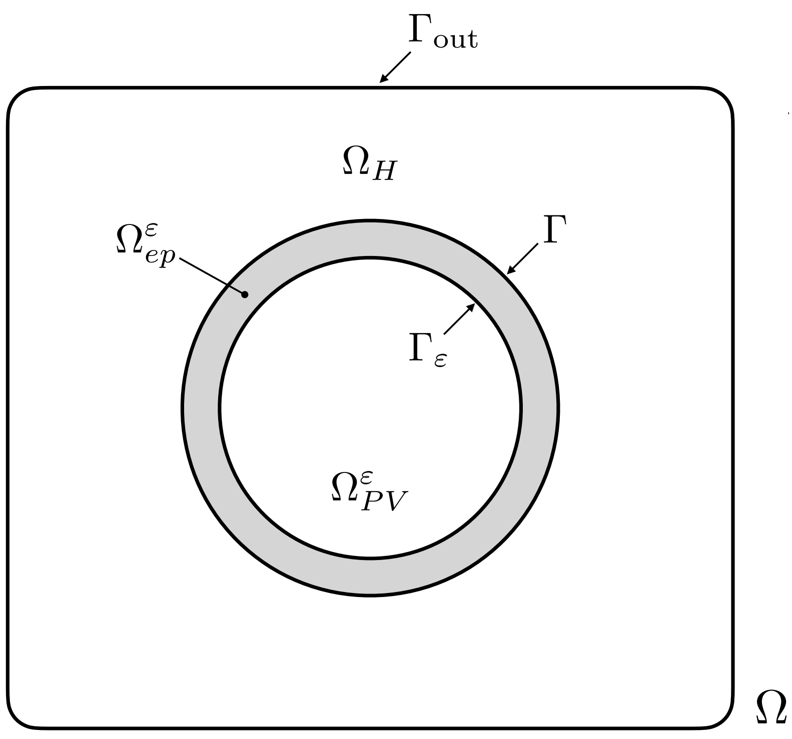
-\nabla\cdot(\sigma_e \nabla u_e^\varepsilon) - A_m S_0\,(u_i^\varepsilon - u_e^\varepsilon) &= 0, && \Omega_{ep}^\varepsilon,
\end{aligned}
$$

$$
\begin{aligned}
[\![u_i^\varepsilon]\!]_\Gamma &= 0, & [\![\sigma_i^\varepsilon \partial_{\mathbf{n}} u_i^\varepsilon]\!]_\Gamma &= 0, & [\![u_e^\varepsilon]\!]_\Gamma &= 0, & [\![\sigma_e \partial_{\mathbf{n}} u_e^\varepsilon]\!]_\Gamma &= 0,\\
[\![u_i^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0, & [\![\sigma_i^\varepsilon \partial_{\mathbf{n}} u_i^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0, & [\![u_e^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0, & [\![\sigma_e \partial_{\mathbf{n}} u_e^\varepsilon]\!]_{\Gamma_\varepsilon} &= 0,
\end{aligned}
$$

$$
\partial_{\mathbf{n}} u^\varepsilon_{i\,|\Gamma_{\text{out}}} = 0, \quad \partial_{\mathbf{n}} u^\varepsilon_{e\,|\Gamma_{\text{out}}} = 0,
$$

$$
\int_\Omega u_e^\varepsilon \, dx = 0.
$$

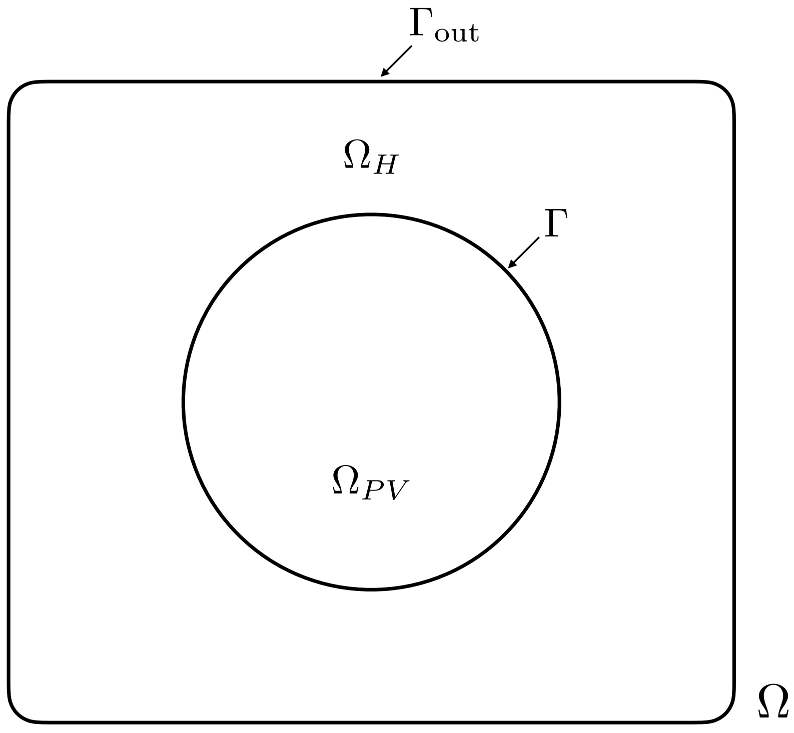


Classical Ansatz

$$
\begin{aligned}
u_{i,e}^\varepsilon(x,y) &= \sum_{p\geq 0} \varepsilon^p u_{i,e}^p(x,y), && \Omega_H \cup \Omega_{PV}^\varepsilon\\
\mathrm{U}_{i,e}^\varepsilon(\xi_1,\eta) &= \sum_{p\geq 0} \varepsilon^p \mathfrak{u}_{i,e}^p(\xi_1,\eta), && \Gamma \times (0,1)
\end{aligned}
$$

Analysis after PFA

The asymptotic analysis: the zero order



Inside the healthy heart Classical Bidomain model

$$
\begin{aligned}
-\nabla\cdot(\sigma_i \nabla u_i^0) + A_m I_{ion}(u_i^0 - u_e^0) &= \mathbb{1}_{\Omega_H} f, \qquad \Omega_H \cup \Omega_{PV},\\
-\nabla\cdot(\sigma_e \nabla u_e^0) - A_m I_{ion}(u_i^0 - u_e^0) &= -\mathbb{1}_{\Omega_H} f, \qquad \Omega_H \cup \Omega_{PV},\\
\partial_{\mathbf{n}} u_i^0|_{\Gamma_{\text{out}}} = 0,\ \partial_{\mathbf{n}} u_e^0|_{\Gamma_{\text{out}}} &= 0,\\
\int_{\Omega_H \cup \Omega_{PV}} u_e^0 dx &= 0.
\end{aligned}
$$

At the interface Γ

$\partial_{\mathbf{n}} u_i^0|_{\Gamma^-} = 0,\ \partial_{\mathbf{n}} u_i^0|_{\Gamma^+} = 0,$ Neumann boundary condition on intra-cellular potential

$[\![u_e^0]\!]_\Gamma = 0,\ [\![\partial_{\mathbf{n}} u_e^0]\!]_\Gamma = 0,$ Continuity on extra-cellular potential

Fully isolated

In the EP area (profile solutions)

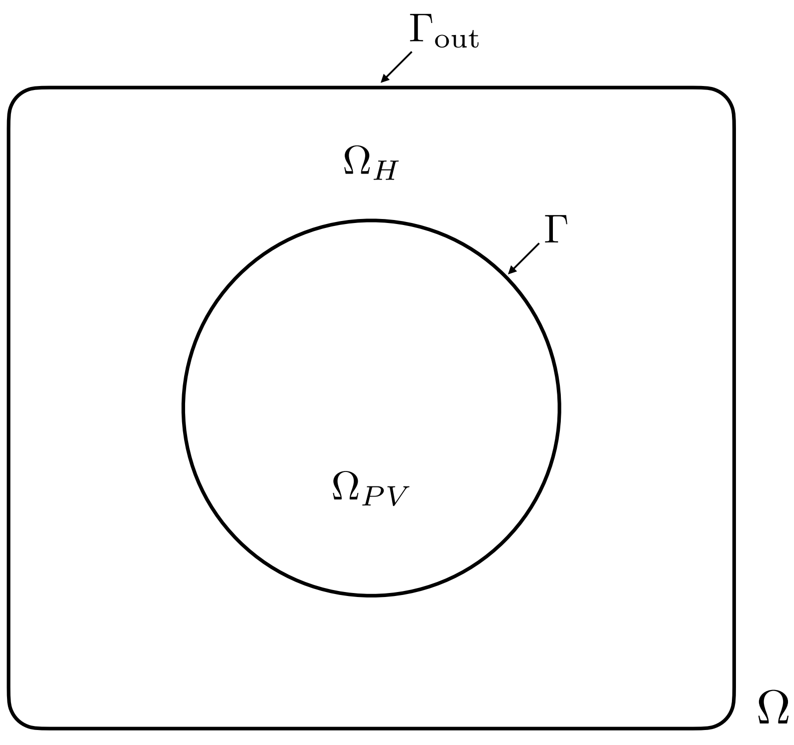
$$
\begin{aligned}
\mathfrak{u}_e^0 &= u_e^0|_{\Gamma^-},\\
\mathfrak{u}_i^0 &= u_e^0|_{\Gamma^-} + \mu_0(\xi_1) e^{-\omega\eta} + \lambda_0(\xi_1) e^{\omega\eta}
\end{aligned}
$$

- Local coordinates (ξ_1, ξ_2)
- Variable change $\eta := \xi_2/\varepsilon$

Analysis after PFA

The asymptotic analysis: the first order

- Curvature $\kappa(\xi_1)$
- Map Φ_ε



At the interface Γ

$$\partial_{\mathbf{n}} u^1_{i\,|_{\Gamma-}} = \partial_\eta \mathfrak{u}^0_{i\,|_{\eta=0}},$$

$$\partial_{\mathbf{n}} u^1_{i\,|_{\Gamma+}} = \partial_\eta \mathfrak{u}^0_{i\,|_{\eta=1}},$$

Not fully isolated!

$$[\![u^1_e]\!]_\Gamma = \partial_{\mathbf{n}} u^0_{e|_{\Gamma-}} - \int_0^1 \int_0^{\bar\eta} \kappa(\xi_1)\partial_s \mathfrak{u}^0_e \, ds d\bar\eta,$$

$$[\![\partial_{\mathbf{n}} u^1_e]\!]_\Gamma = \kappa(\xi_1)\Big[-\partial_{\mathbf{n}} u^0_{e|_{\Gamma-}} + \int_0^1 \int_0^{\bar\eta} \kappa(\xi_1)\partial_s \mathfrak{u}^0_e \, ds d\bar\eta\Big] - \int_0^1 \Big[\frac{A_m S_0}{\sigma_e}(\mathfrak{u}^0_i - \mathfrak{u}^0_e) - (\kappa(\xi_1))^2 \eta \partial_\eta \mathfrak{u}^0_e + S^0_\Gamma \mathfrak{u}^0_e\Big] d\eta.$$

We can now write **effective transmission conditions** for $\tilde{u}^1_{i,e} = u^0_{i,e} + \varepsilon u^1_{i,e}$

Solutions at any order are determined by induction.

The asymptotic analysis: convergence theorem [1]

Assuming the well-posedness of all the PDE systems and let $(u_i^{\varepsilon,N}, u_e^{\varepsilon,N})$ be the functions defined by

$$u_{i,e}^{\varepsilon,N} = \begin{cases} \sum_{k=0}^{N} \varepsilon^k u_{i,e}^k, & \Omega_H \cup \Omega_{PV}^{\varepsilon}, \\ \sum_{k=0}^{N} \varepsilon^k \mathfrak{u}_{i,e}^k \circ \Phi_{\varepsilon}^{-1}, & \Omega_{ep}^{\varepsilon}, \end{cases}$$

for all $N > 0$, there exists a constant C_N independent of ε

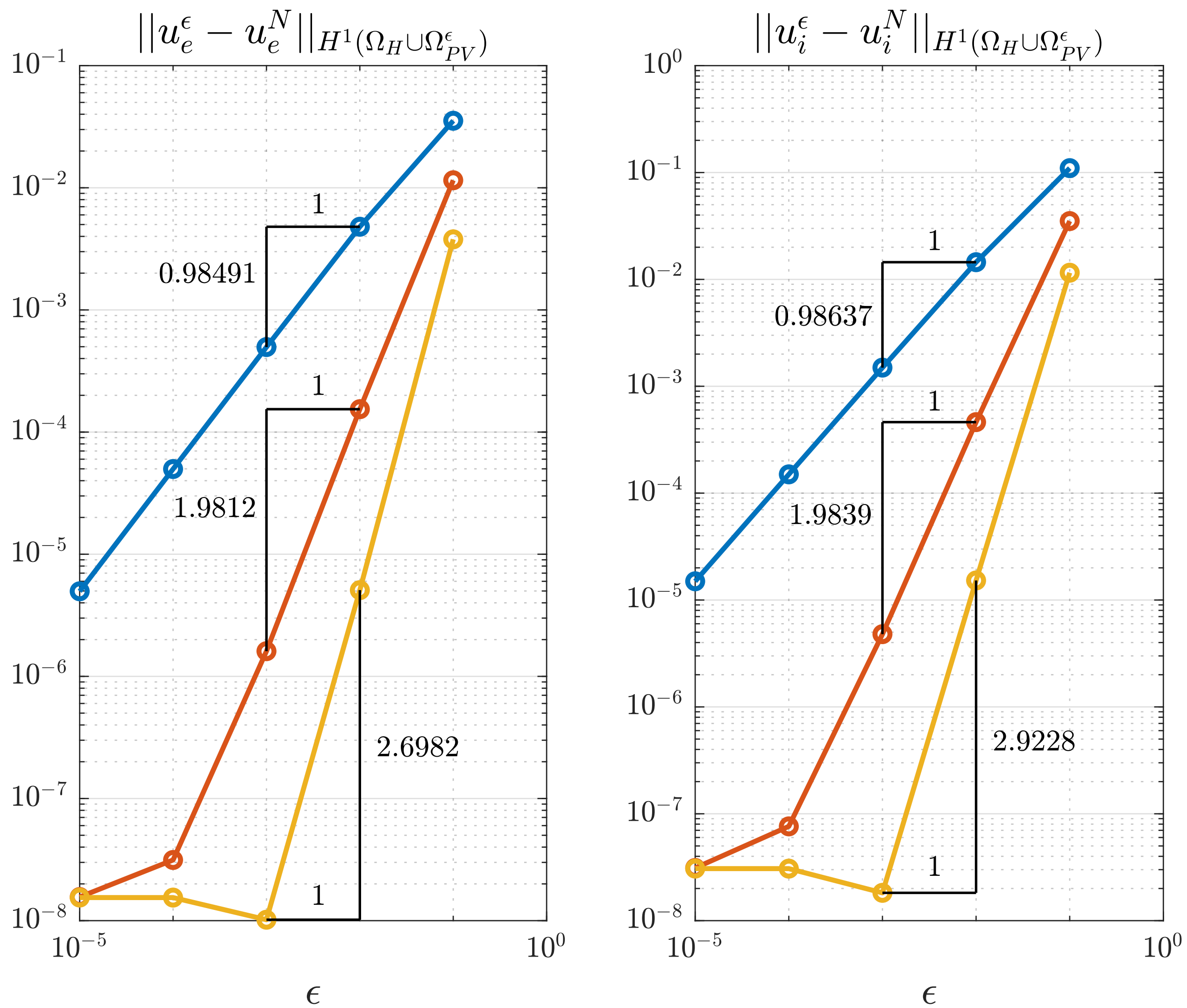
such that

$$\|u_i^{\varepsilon} - u_i^{\varepsilon,N}\|_{H^1(\Omega_H \cup \Omega_{PV}^{\varepsilon})} + \|u_e^{\varepsilon} - u_e^{\varepsilon,N}\|_{H^1(\Omega)} + \varepsilon \|\nabla(u_i^{\varepsilon} - u_i^{\varepsilon,N})\|_{L^2(\Omega_{ep}^{\varepsilon})} \leq C_N \varepsilon^{N+1}.$$

[1] A. Collin, S. Nati Poltri, C. Poignard. Electrocardiology modeling after pulsed field ablation relying on asymptotic analysis. To be submitted. 2024.

Analysis after PFA

The asymptotic analysis: convergence theorem [1]



Numerical validation through convergence tests for the zero and first orders

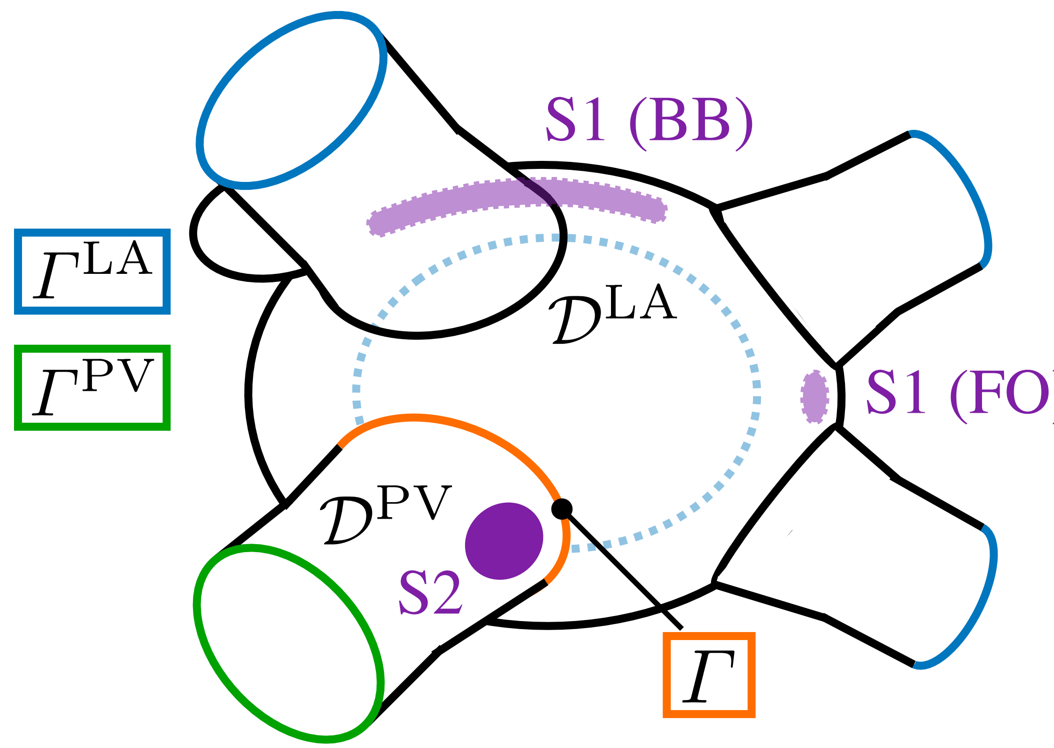
$$\|u_i^\varepsilon - u_i^{\varepsilon,N}\|_{H^1(\Omega_H \cup \Omega_{PV}^\varepsilon)} + \|u_e^\varepsilon - u_e^{\varepsilon,N}\|_{H^1(\Omega)} + \varepsilon \|\nabla(u_i^\varepsilon - u_i^{\varepsilon,N})\|_{L^2(\Omega_{ep}^\varepsilon)} \leq C_N \varepsilon^{N+1}.$$

[1] A. Collin, S. Nati Poltri, C. Poignard. Electrocardiology modeling after pulsed field ablation relying on asymptotic analysis. To be submitted. 2024.

RFA vs PFA

Coming back to the dynamical system…

$$A_m(C_m\partial_t v_m + I_{ion}(v_m,w)) - \nabla\cdot(\bar{\bar{\sigma}}_i\cdot\nabla u_i) = 0,$$
$$\nabla\cdot(\bar{\bar{\sigma}}_e\cdot\nabla u_e) + \nabla\cdot(\bar{\bar{\sigma}}_i\cdot\nabla u_i) = 0,$$
$$\partial_t w + g(v_m,w) = 0,$$
$$v_m = u_i - u_e,$$



$$\mathcal{D} = \mathcal{D}^{\mathrm{LA}} \cup \Gamma \cup \mathcal{D}^{\mathrm{PV}}$$

with homogeneous Neumann BC on $\partial\mathcal{D}$

$$(\bar{\bar{\sigma}}_i\cdot\nabla u_i)\cdot\bar{n} = 0, \quad (\bar{\bar{\sigma}}_e\cdot\nabla u_e)\cdot\bar{n} = 0,$$

and conductivity tensors [1] defined as

$$\bar{\bar{\sigma}}_{i,e} = \sigma^t_{i,e}\bar{\bar{I}} + (\sigma^t_{i,e} - \sigma^l_{i,e})\left[I_0(\theta)\bar{\tau}_0\otimes\bar{\tau}_0 + J_0(\theta)\bar{\tau}_0^\perp\otimes\bar{\tau}_0^\perp\right]$$

The EP area is reduced to an interface!

and transmission conditions on Γ to close the system.

[1] Chapelle, D., Collin, A., & Gerbeau, J. F. (2013). A surface-based electrophysiology model relying on asymptotic analysis and motivated by cardiac atria modeling. *Mathematical Models and Methods in Applied Sciences*, *23*(14), 2749-2776.

RFA vs PFA

…and transmission conditions on Γ to close the system.

RFA: Kedem-Katchalsky conditions.

$$\alpha[\![u_e]\!]_{|\Gamma} = \left((\bar{\bar{\sigma}}_e \cdot \nabla u_e) \cdot \bar{n}\right)_{|\Gamma+} = \left((\bar{\bar{\sigma}}_e \cdot \nabla u_e) \cdot \bar{n}\right)_{|\Gamma-}$$

$$\alpha[\![u_i]\!]_{|\Gamma} = \left((\bar{\bar{\sigma}}_i \cdot \nabla u_i) \cdot \bar{n}\right)_{|\Gamma+} = \left((\bar{\bar{\sigma}}_i \cdot \nabla u_i) \cdot \bar{n}\right)_{|\Gamma-}$$

$\alpha = 0$	Perfect Isolation
$0 < \alpha < 1$	**Fibrosis**
$\alpha \gg 1$	Continuity

PFA: zero order transmission conditions

(i) Continuity of extra-cellular potential and its derivative

$$[\![u_e]\!]_{|\Gamma} = 0, \ \ [\![(\bar{\bar{\sigma}}_e \cdot \nabla u_e) \cdot \bar{n}]\!]_{|\Gamma} = 0$$

(ii) Isolation of intra-cellular potential

$$\left((\bar{\bar{\sigma}}_i \cdot \nabla u_i) \cdot \bar{n}\right)_{|\Gamma+} = \left((\bar{\bar{\sigma}}_i \cdot \nabla u_i) \cdot \bar{n}\right)_{|\Gamma-} = 0$$

RFA vs PFA

[1] Electrocardiology Modeling after Catheter Ablations for Atrial Fibrillation. S. Nati Poltri, G. Caluori, P. Jaïs, A. Collin, C. Poignard. FIMH 2023.

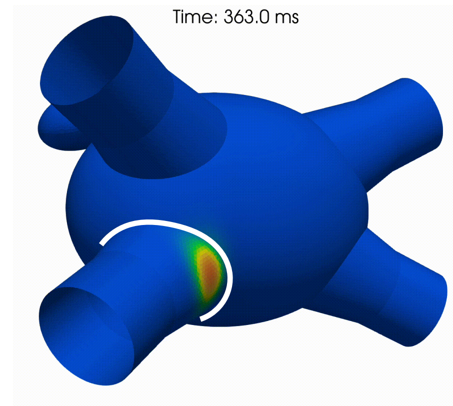
Numerical simulations [1]:

- Numerical resolution: Finite Element Method, BDF 2, FreeFEM++
- Non-overlapping Schwarz-type algorithm for PFA (penalty parameter chosen very carefully through a mathematical study)
- Weak coupling for RFA
- Mesh, fibers and codes are available here: https://gitlab.inria.fr/snatipol/af-pfa-rfa

RFA vs PFA

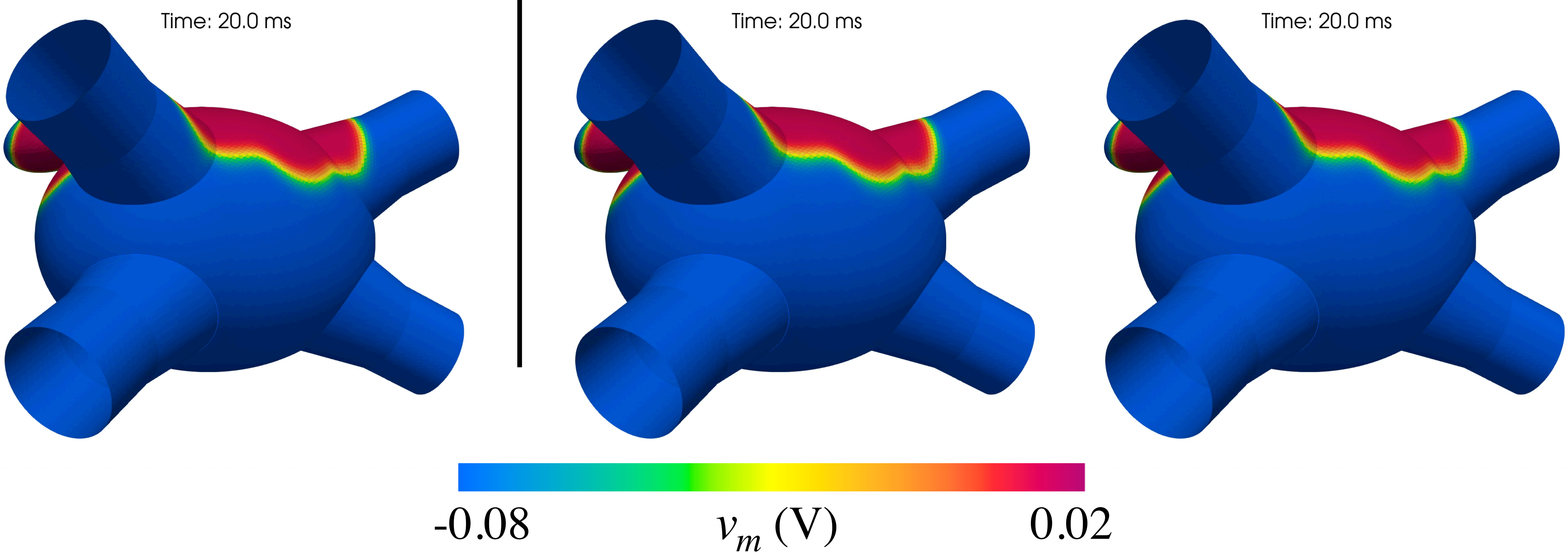
Numerical simulations [1]:

Transmembrane potential



[1] Electrocardiology Modeling after Catheter Ablations for Atrial Fibrillation. S. Nati Poltri, G. Caluori, P. Jaïs, A. Collin, C. Poignard. FIMH 2023.

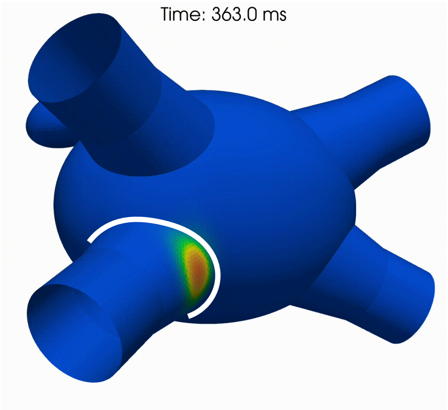
AF | **RFA** $(\alpha = 10^{-4})$ | **PFA**



RFA vs PFA

Numerical simulations [1]:

Transmembrane potential



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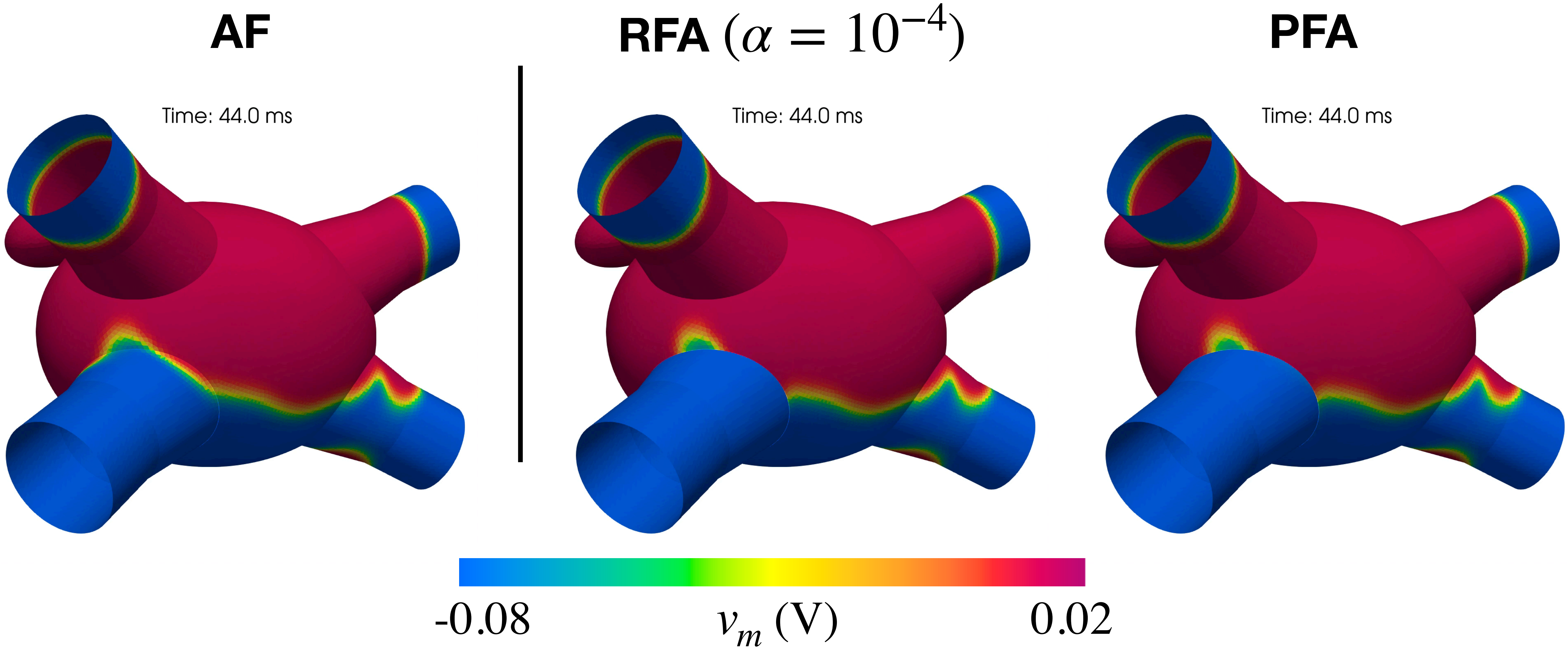
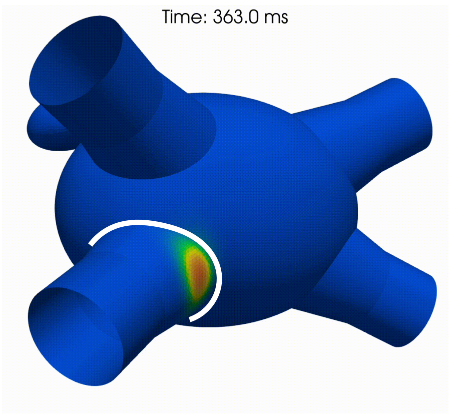


RFA vs PFA

Numerical simulations [1]:

Transmembrane potential



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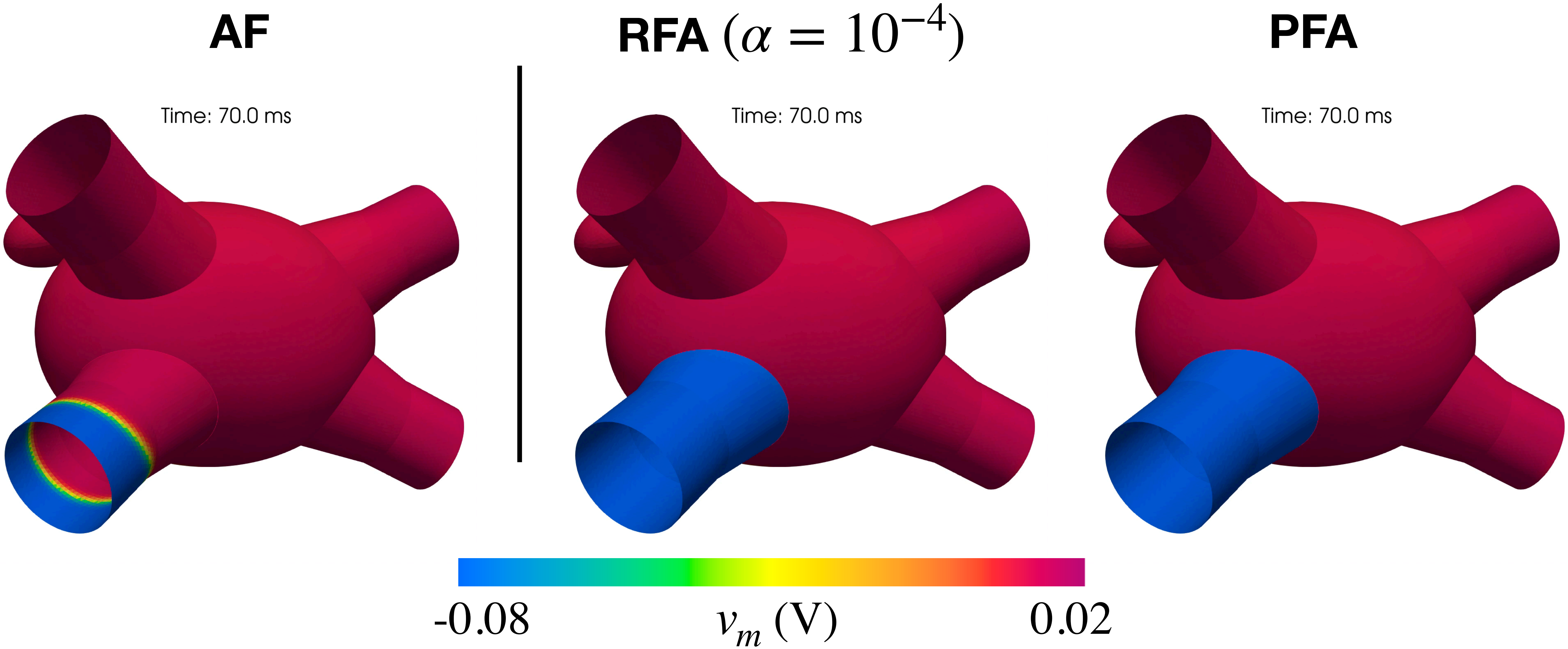
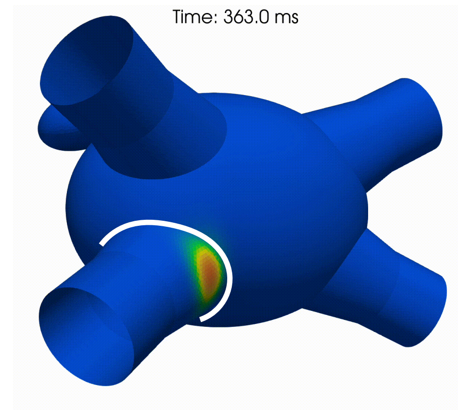


RFA vs PFA

Numerical simulations [1]:

Transmembrane potential



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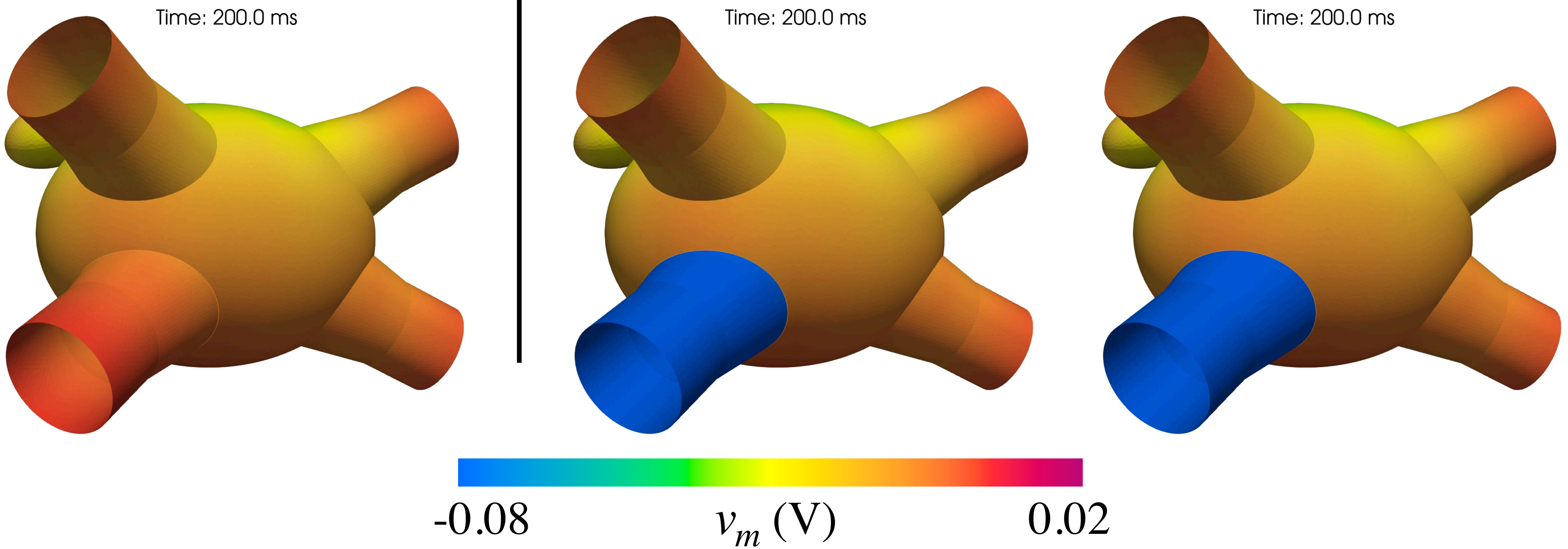
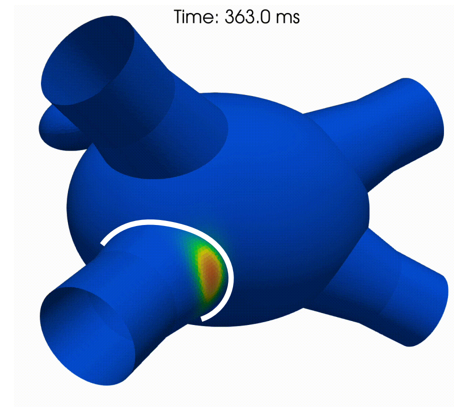
AF | **RFA** ($\alpha = 10^{-4}$) | **PFA**



RFA vs PFA

Numerical simulations [1]:

Transmembrane potential



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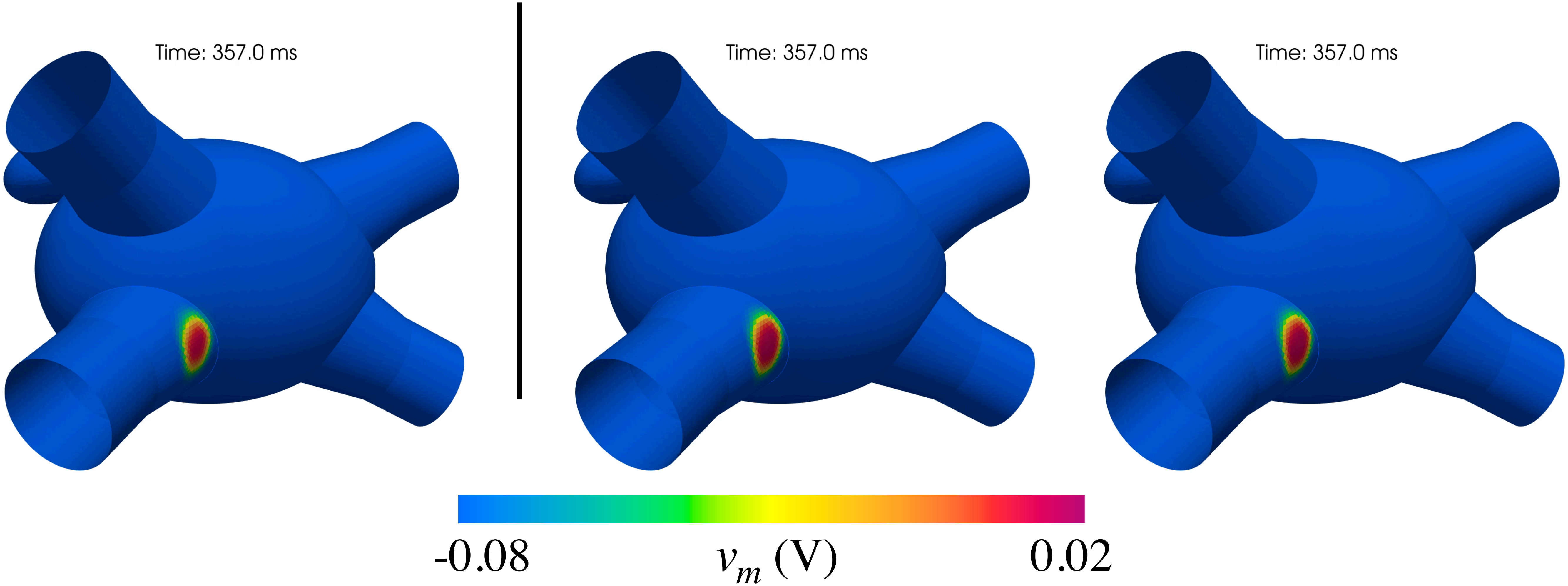
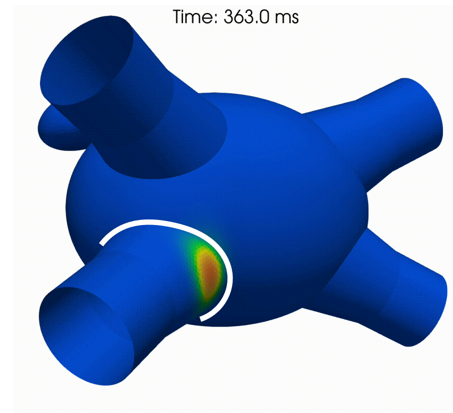


Numerical simulations [1]:

Transmembrane potential



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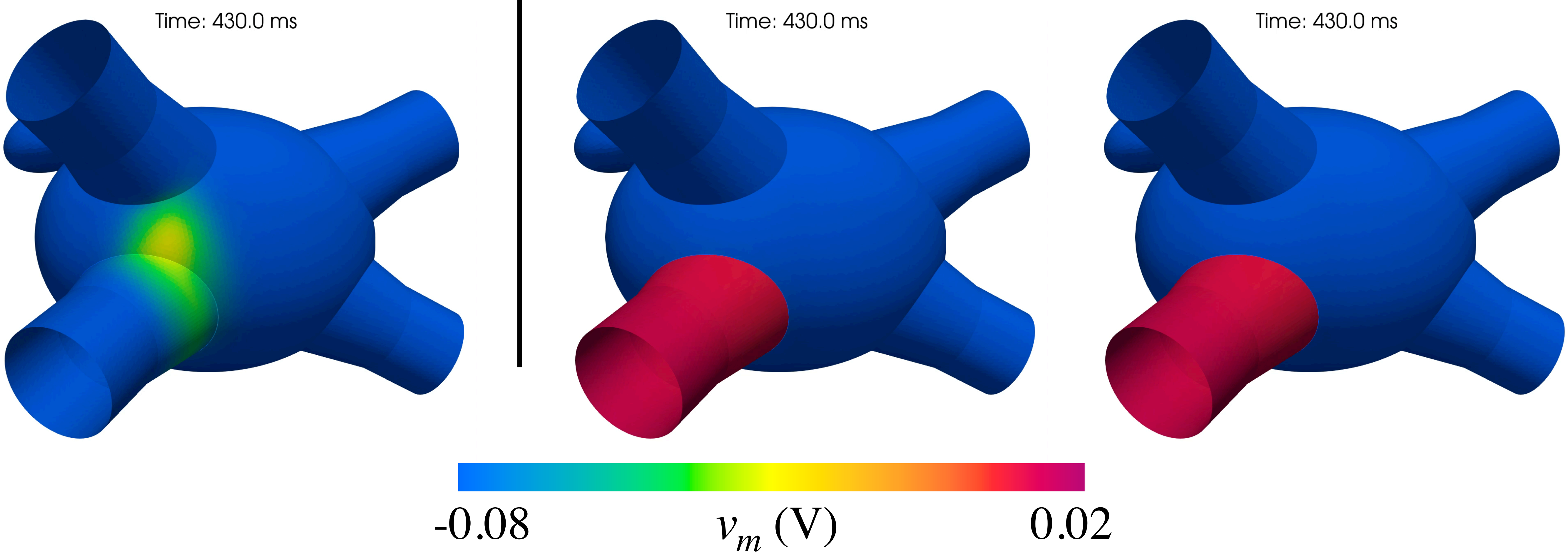
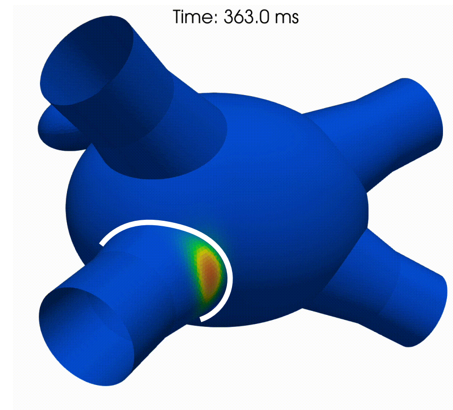


RFA vs PFA

Numerical simulations [1]:

Transmembrane potential



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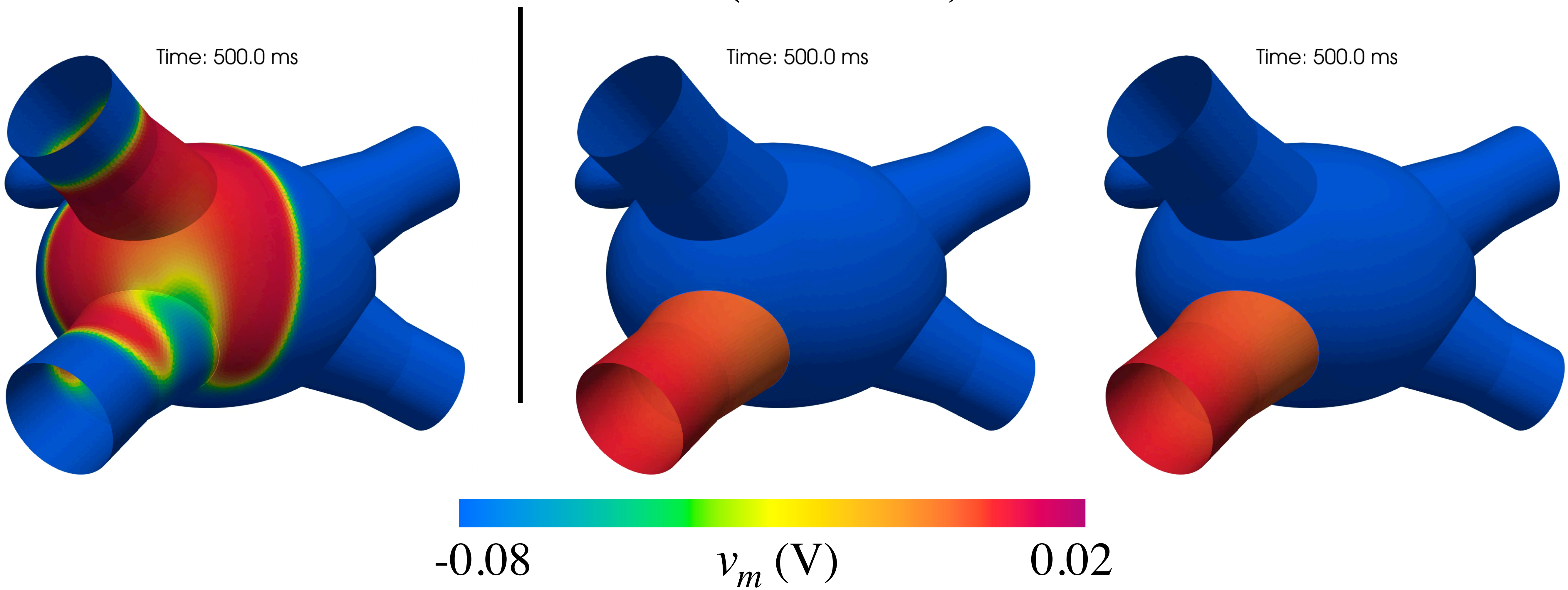
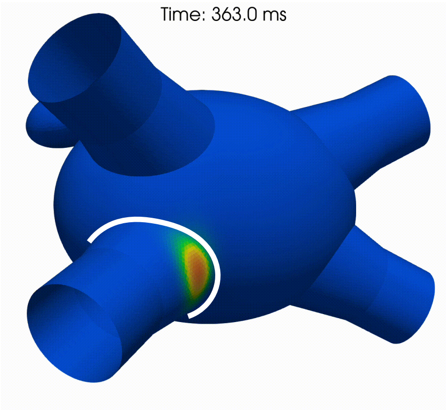


RFA vs PFA

Numerical simulations [1]:



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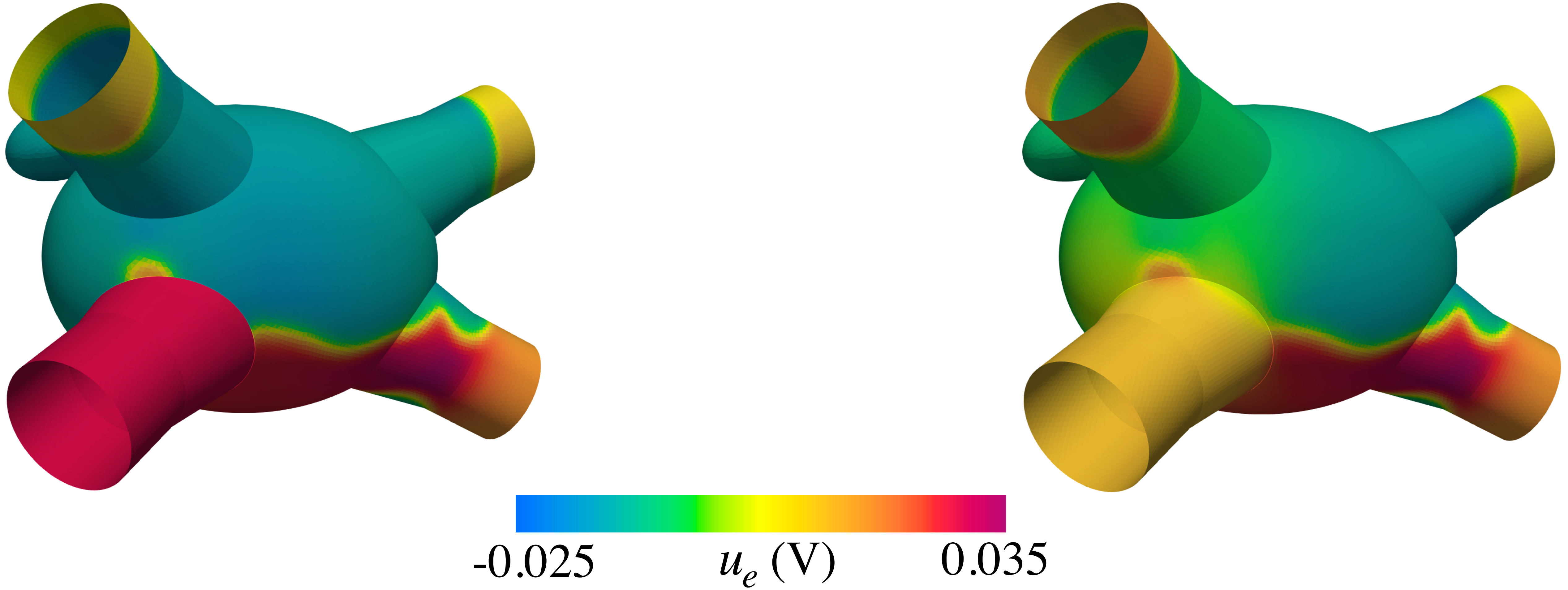
Extra-cellular potential

RFA: quasi-complete decoupling of the two domains for all potentials (intra- and extra-cellular potentials)

PFA: continuity of extracellular potential (Only the cardiomyocytes are impacted)



RFA vs PFA

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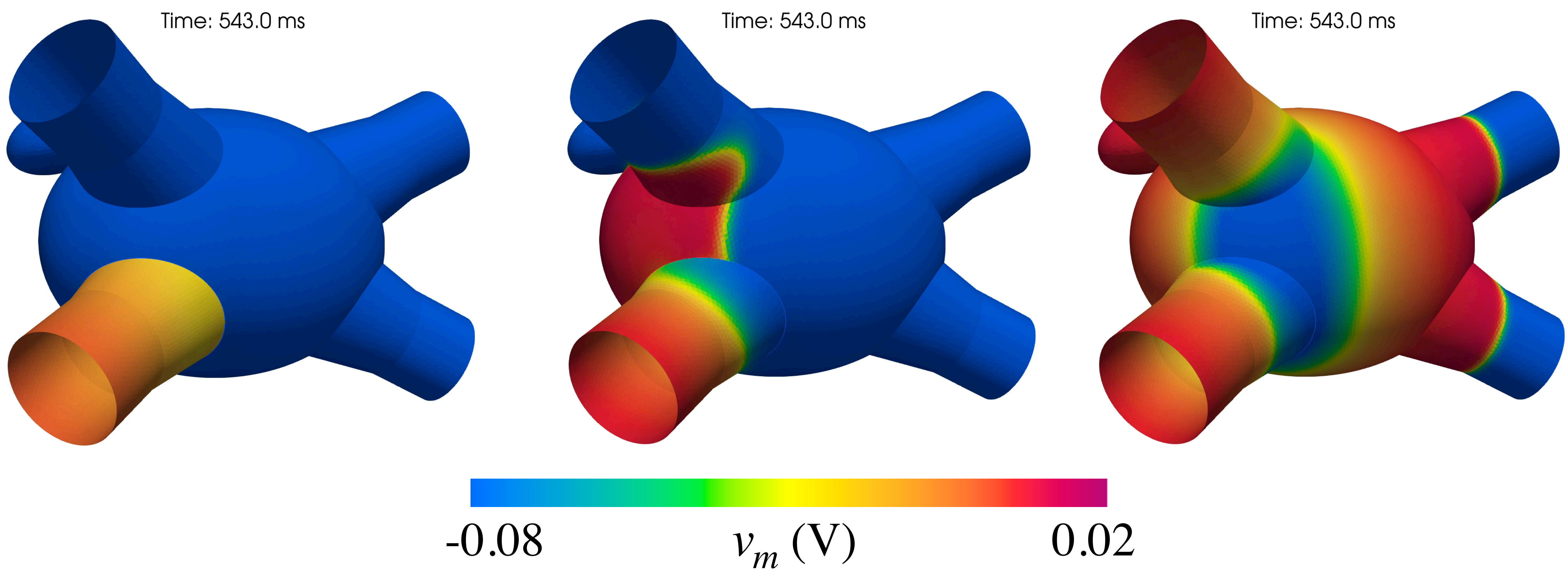
Numerical simulations [1]:

RFA-induced fibrosis

RFA $(\alpha = 10^{-4})$ — Perfect isolation

RFA $(\alpha = 10^{-3})$

RFA $(\alpha = 10^{-2})$ — Partial disconnection



Conclusion

Conclusion

- Asymptotic analysis of the static bidomain problem containing an EP area, treated by PFA
- Comparaison of model and simulations of RFA and PFA

Clinical Perspective (animal or patient data)

- Extract geometry & catheter position from medical images
- Determine the electroporated area with a tissue PFA modeling (@Simon Bihoreau)
- Validate our model by comparing activation time obtained with our model with measured activation time after electroporation
- Final objective: predict the activation times depending the catheter position etc…

Thank you for the attention