PhD Modeling life science I - Dynamical processes

Mathematics of differential equations - Lecture

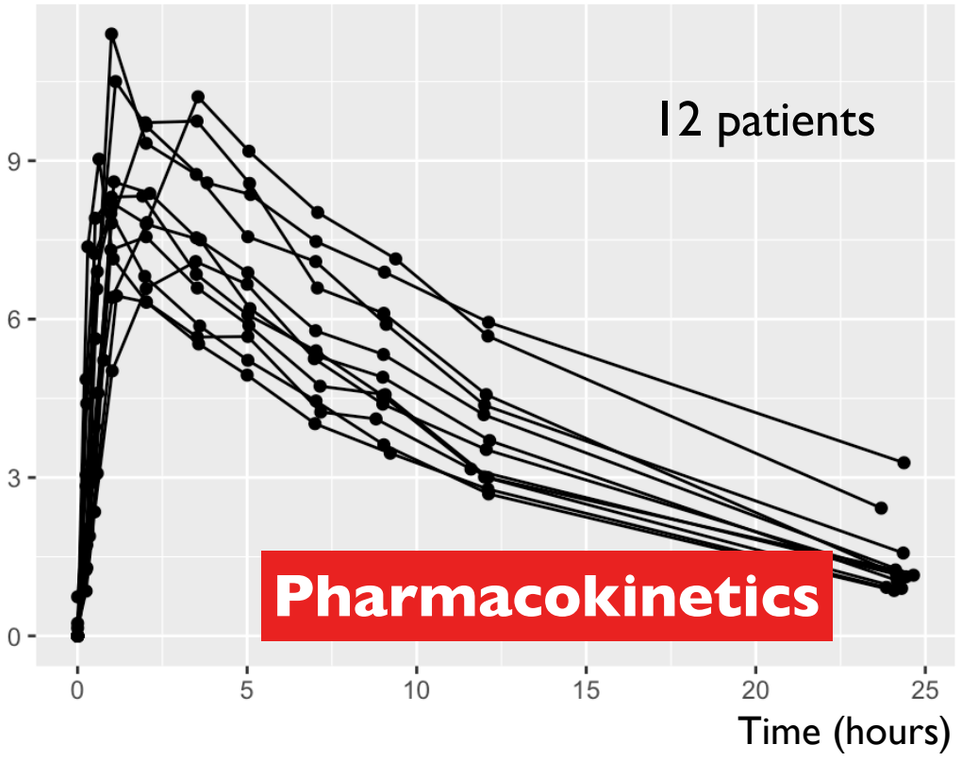
Annabelle Collin

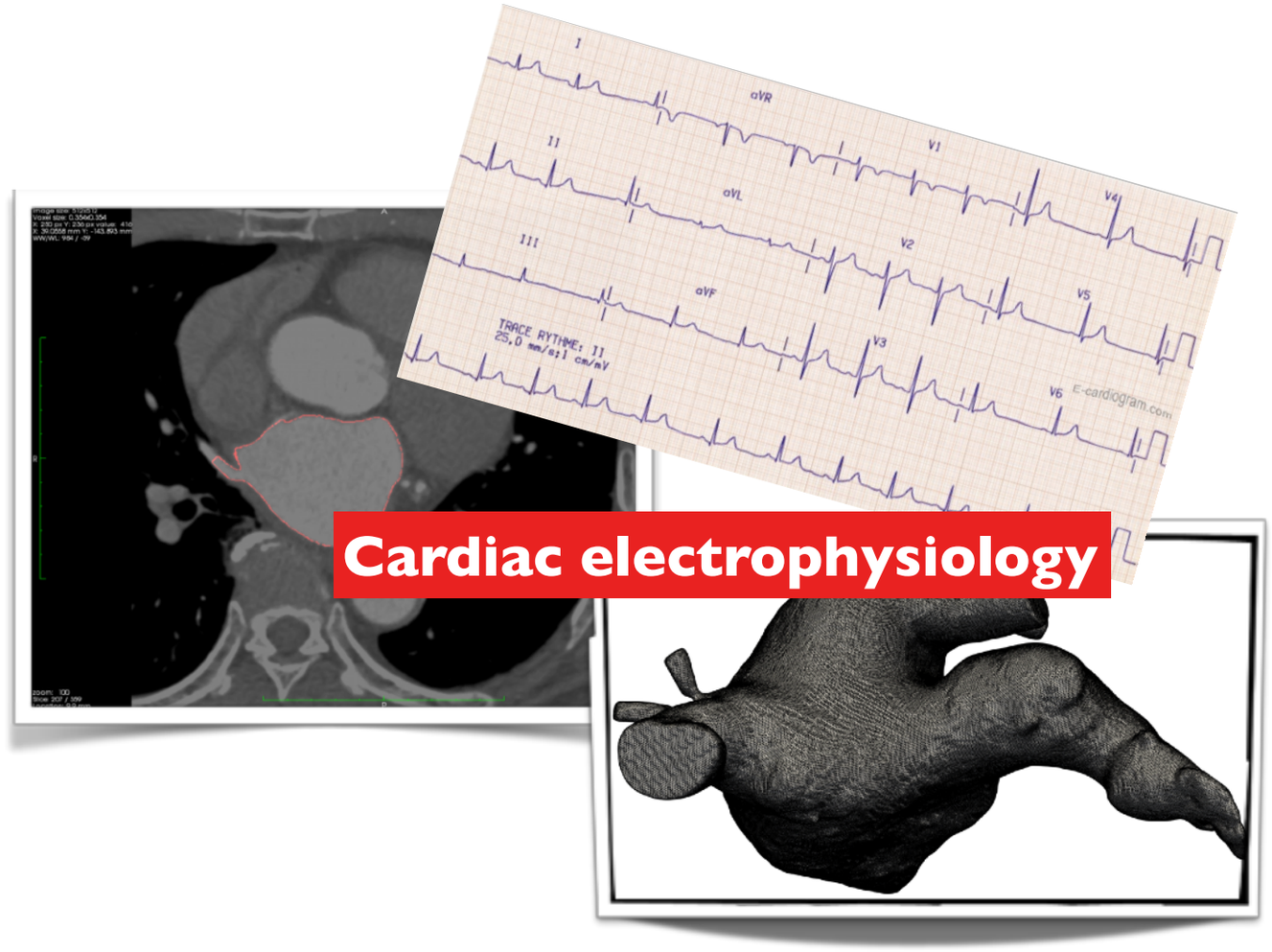
Introduction

Introduction

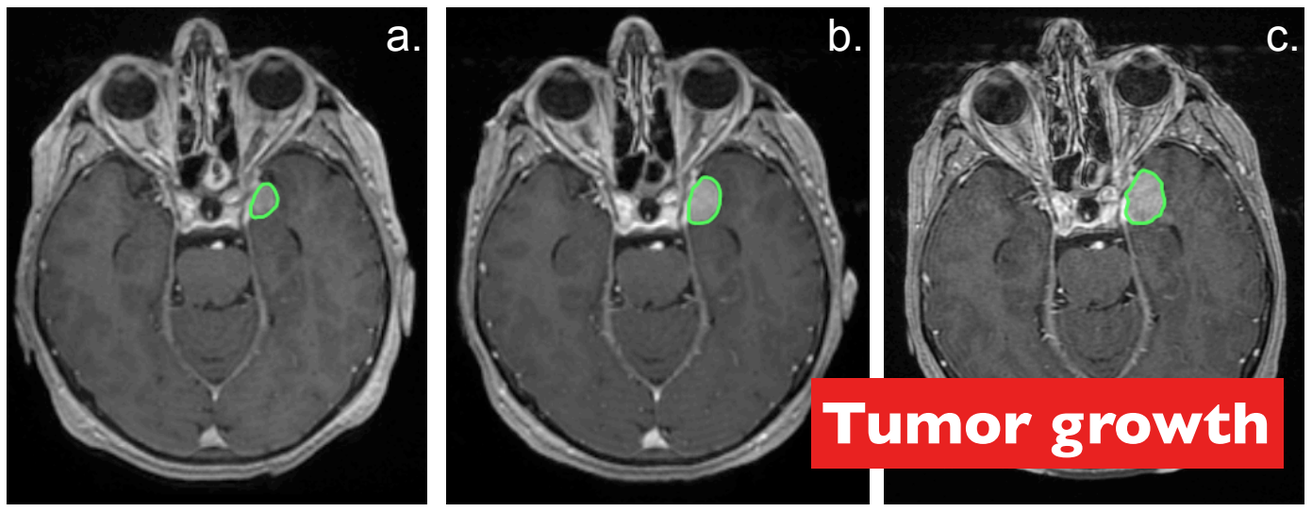
- Medical data

Concentration plasma (mg/L)





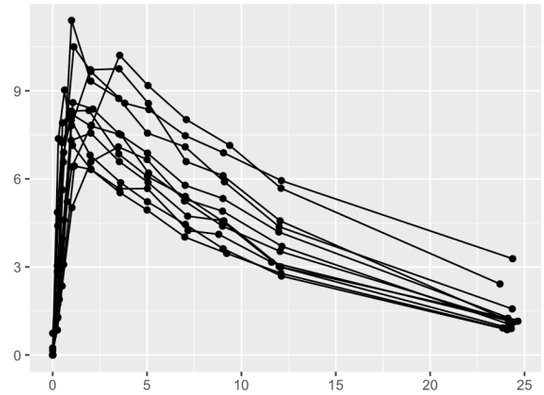
CHU Bordeaux - MRI T1 (with gadolinium contrast agent)

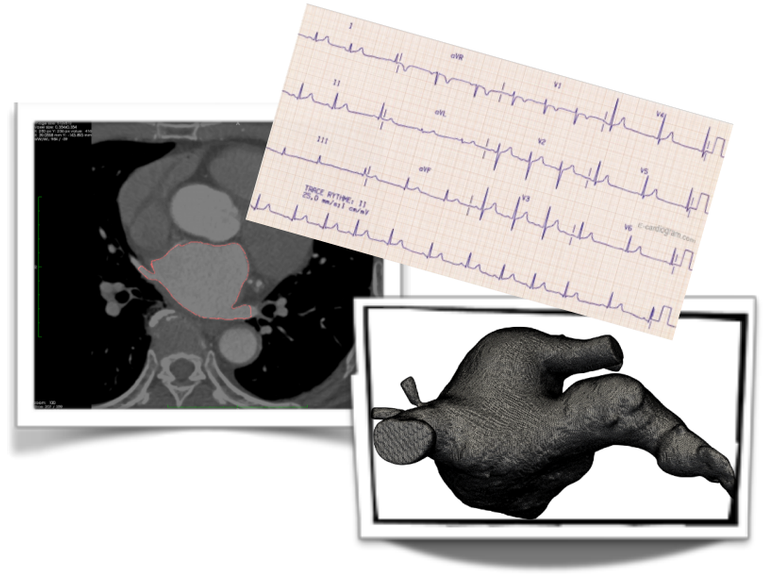


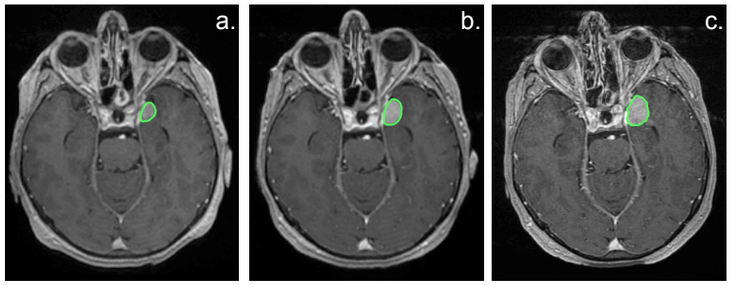
Introduction

- Link between all these phenomena?

  Temporal evolution of some quantities …
  Dynamic process







- Can we model these processus?

  Yes: using physical or biological laws …

  Lead to Ordinary Differential Equations or Partial Differential Equations

  if spatial aspects!

- And why?

  Very important: What is the **clinical** question?

  Objective: help clinicians to establish a diagnosis ; to improve the patient follow-up: surgery? treatment? …

Introduction

- Step 0: Define a specific clinical question
- Step 1: Write a model (or models…)
- Step 2: Mathematical study of the solution of the model
- Step 3: Approximation of the solution using a numerical scheme (in case of non explicit solution)
- Step 4: Patient-specific simulation using available data

Presentation of the strategy based on 3 examples:

- Pharmacokinetics
- Cardiac electrophysiology
- Tumor growth

Modeling

Modeling: pharmacokinetics

- Pharmacokinetics one-compartment model with first-order absorption and elimination

$$\begin{cases} \dot{A}_{GI} = -k_a A_{GI} \\ \dot{U}_P = \frac{k_a}{V_0} A_{GI} - k_e U_P \end{cases}$$

temporal evolutions

A_{GI} Dose in Gastro-intertinal compartment (mg)

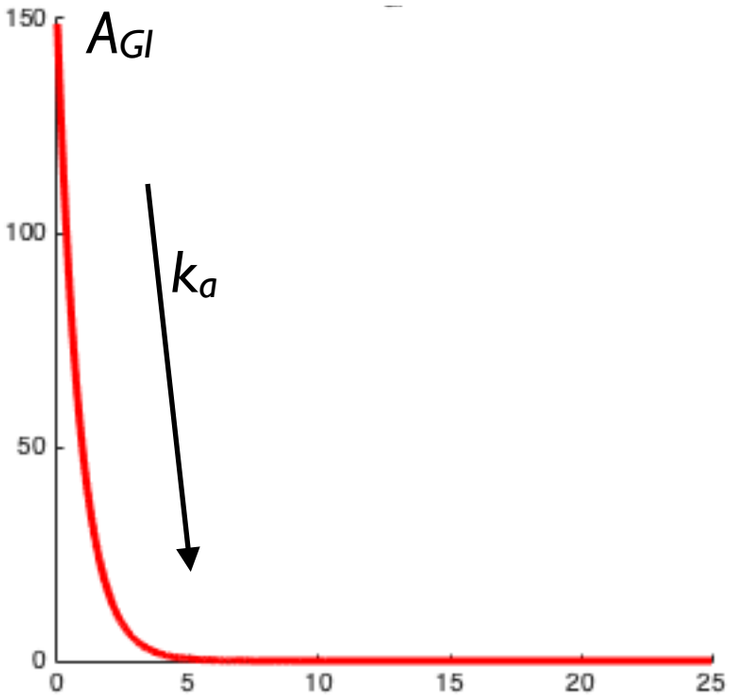
U_P Concentration Plasma compartment (mg/L)

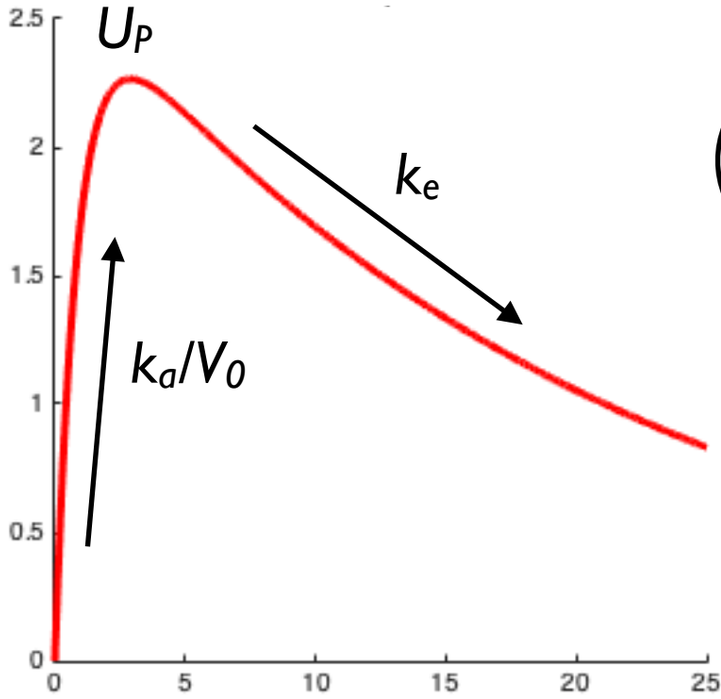
k_a Drug absorption rate (h^{-1})

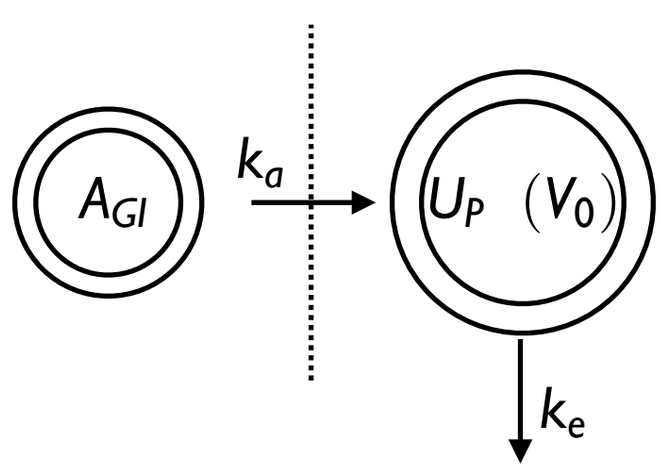
k_e Drug elimination rate (h^{-1})

V_0 Volume of distribution (L)

Linear ODE
Conservation laws







Clinical question: pharmacokinetics

- Pharmacokinetics one-compartment model with first-order absorption and elimination

$$\begin{cases} \dot{A}_{GI} = -k_a A_{GI} \\ \dot{U}_P = \frac{k_a}{V_0} A_{GI} - k_e U_P \end{cases}$$

temporal evolutions

A_{GI} Dose in Gastro-intertinal compartment (mg)

U_P Concentration Plasma compartment (mg/L)

k_a Drug absorption rate (h^{-1})

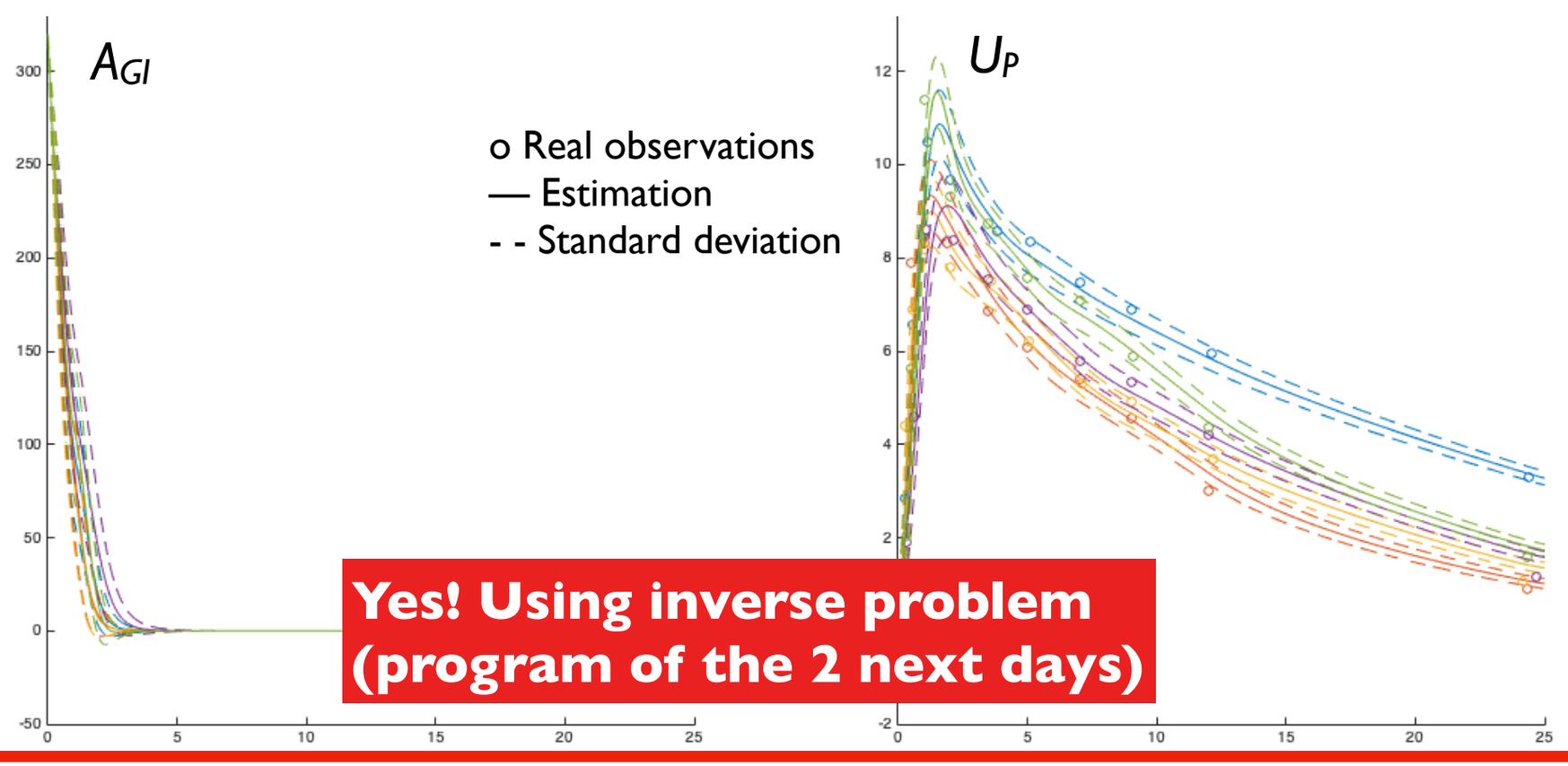
k_e Drug elimination rate (h^{-1})

V_0 Volume of distribution (L)

Linear ODE
Conservation laws

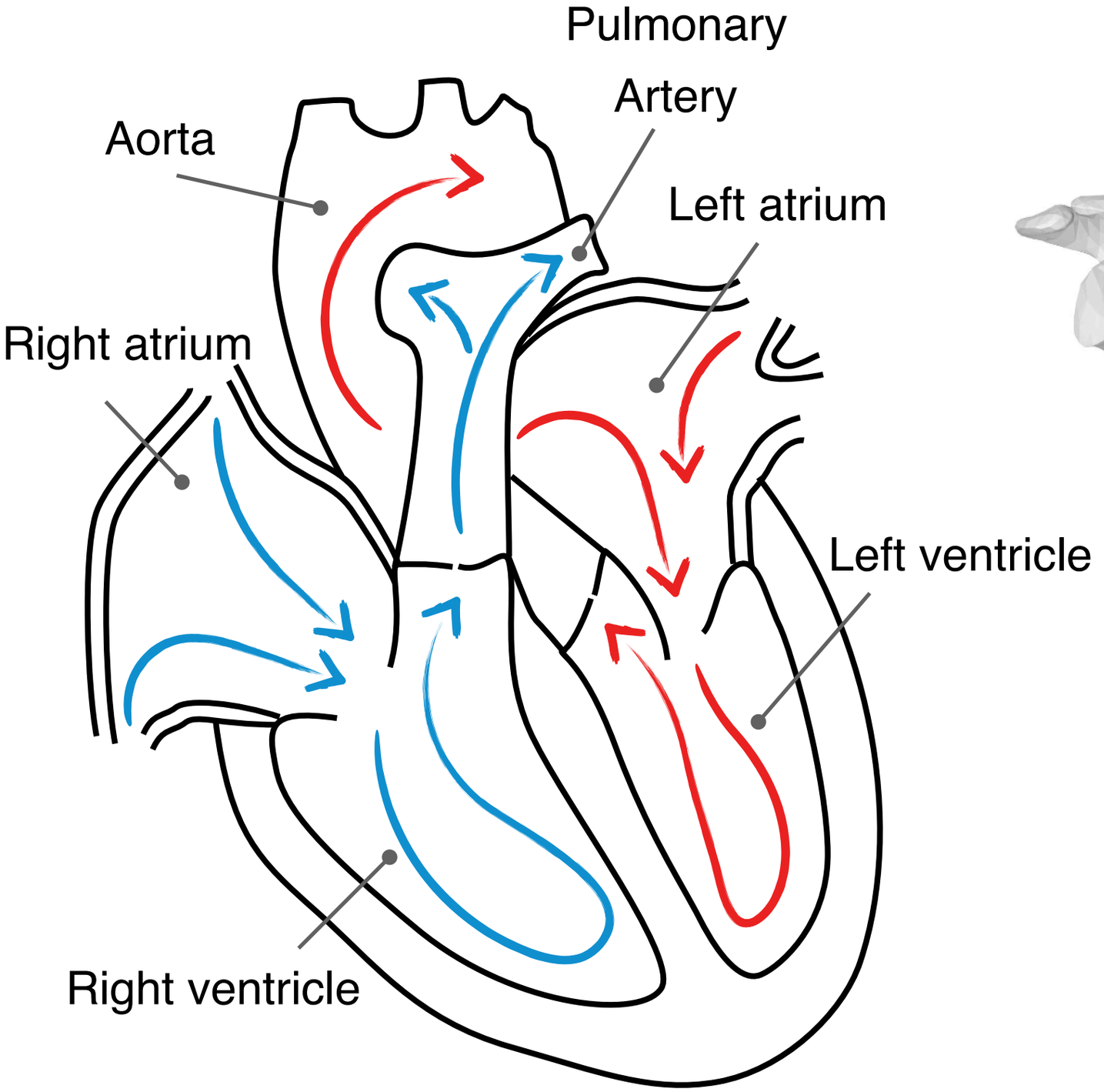
- Using time-sampled observations of U_P, can we estimate the parameters k_a, k_e, and V_0 and then personalise the treatment by adapting the dose for instance?

k_a	k_e	V_0
0.6924	-3.0547	3.4033
0.7421	-2.3973	3.4982
0.6923	-2.5440	3.5403
0.3292	-2.6008	3.4775
0.6262	-2.5827	3.2786
0.3073	-2.5252	3.8100
-0.1602	-2.5062	3.5986
0.3842	-2.5088	3.6314
1.3929	-2.6230	3.7059
-0.3844	-2.6935	3.2786
1.0531	-2.4339	3.6792
0.0366	-2.4369	3.2556

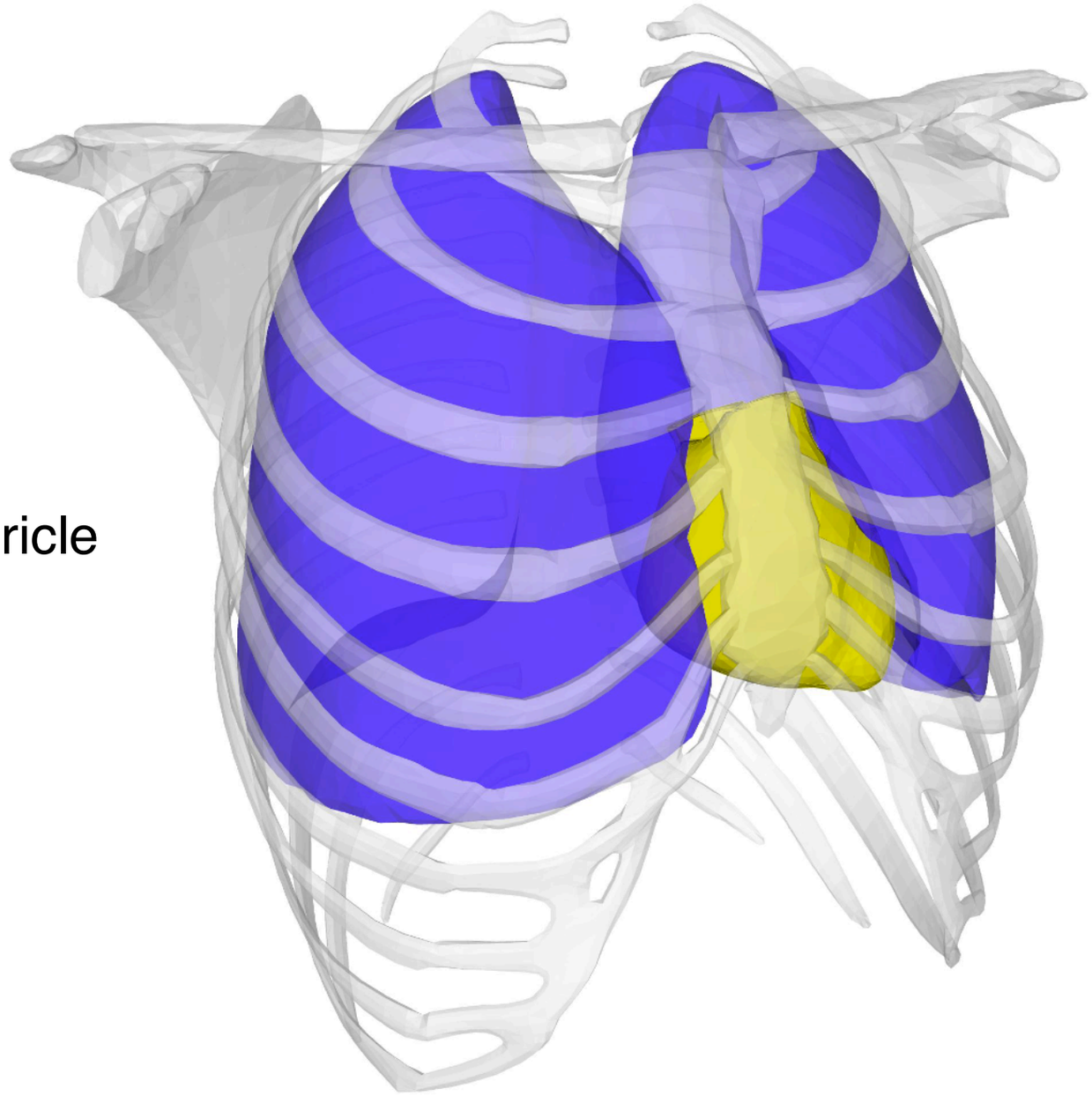


Yes! Using inverse problem (program of the 2 next days)

Modeling: cardiac electrophysiology



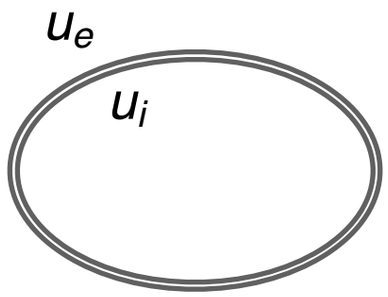
Blood circulation in the heart



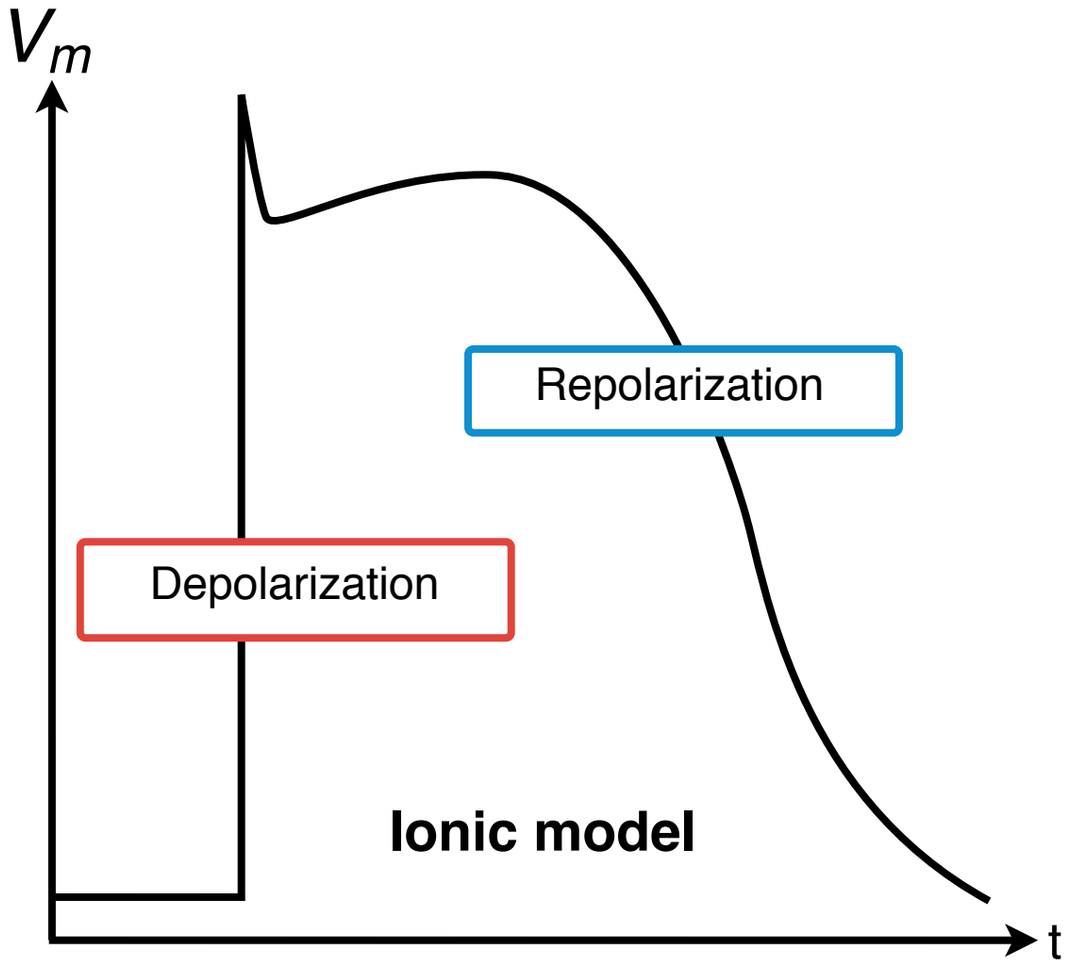
Electrical activity = origin of the mechanical activity

Modeling: cardiac electrophysiology

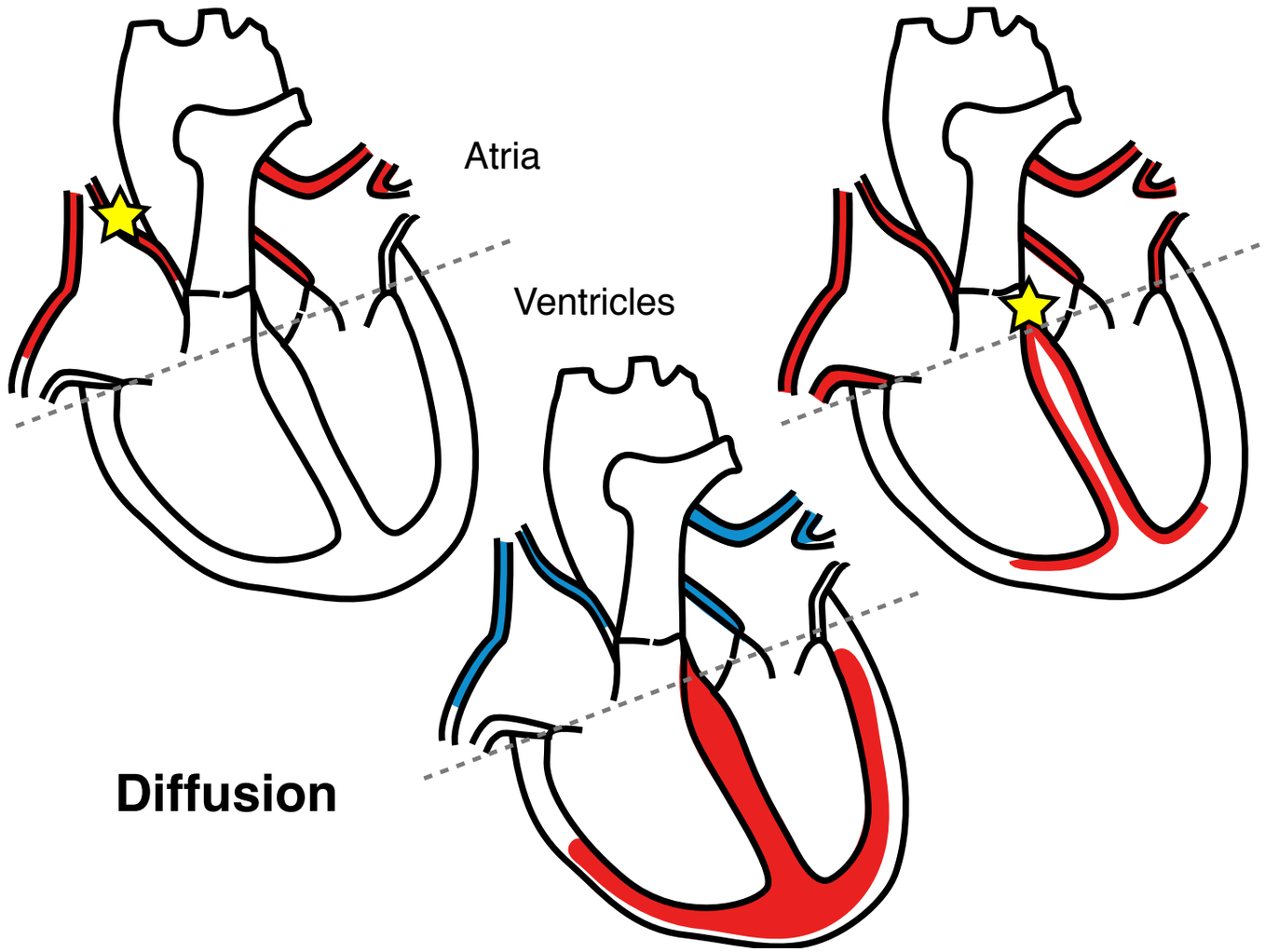
- Two modeling scales



$V_m = u_i - u_e$



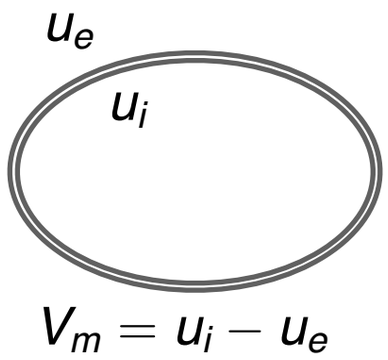
Ionic model

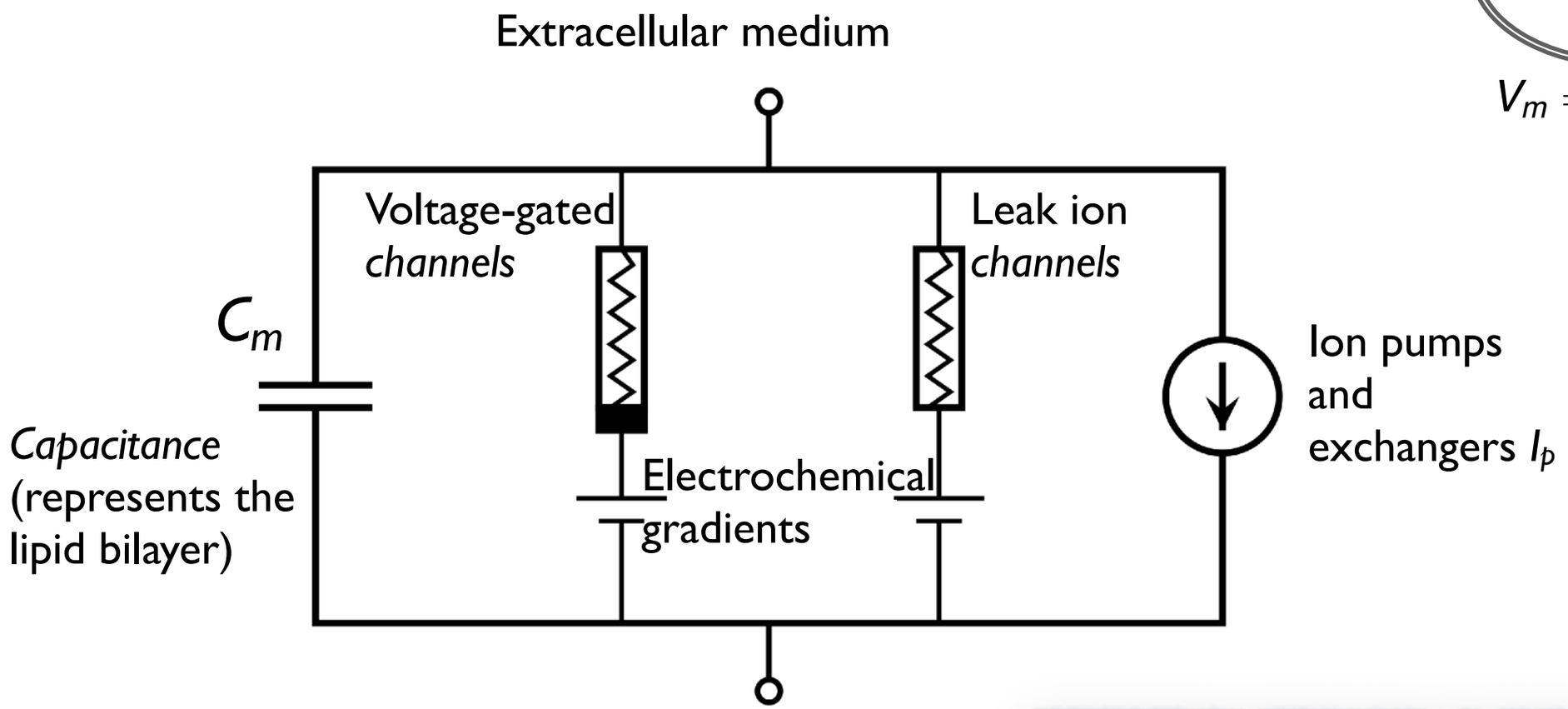


Diffusion

Modeling: cardiac electrophysiology

- Cell scale: ionic model





Hodgkin, A. L., & Huxley, A. F. (1952). Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *The Journal of physiology*, *116*(4), 449-472.

Hodgkin–Huxley type models represent the biophysical characteristic of cell membranes

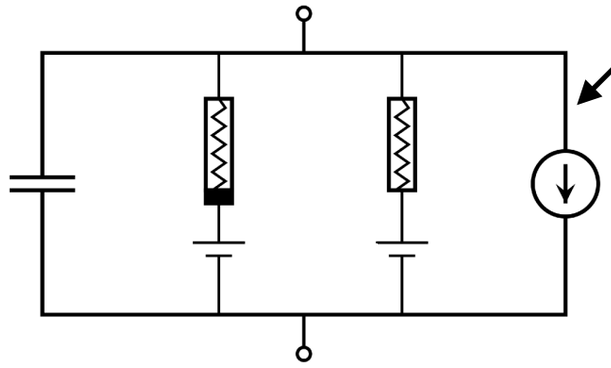
Modeling: cardiac electrophysiology

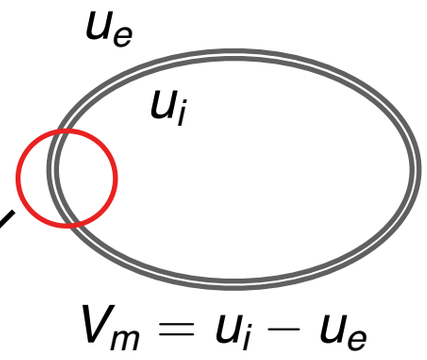
- Cell scale: ionic model

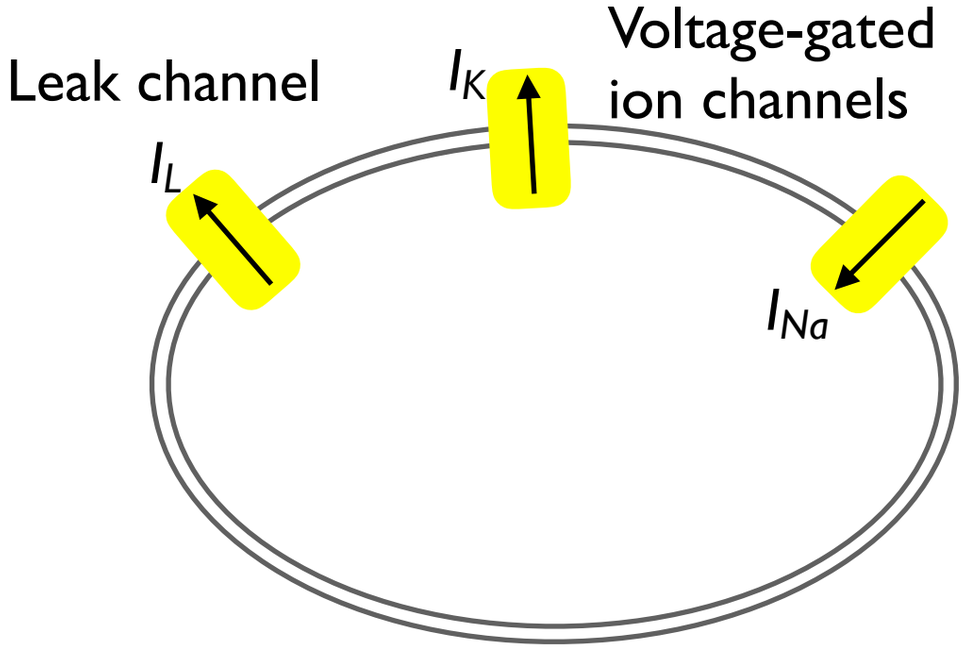
$$I = C_m \dot{V}_m + I_{ion}$$

$$\dot{p} = \alpha_p(V_m)(1 - p) - \beta_p(V_m)p, \quad p = n, m, h$$

$$I_{ion} = g_K n^4 (V_m - V_K) + g_{Na} m^3 h (V_m - V_{Na}) + g_l (V_m - V_l)$$





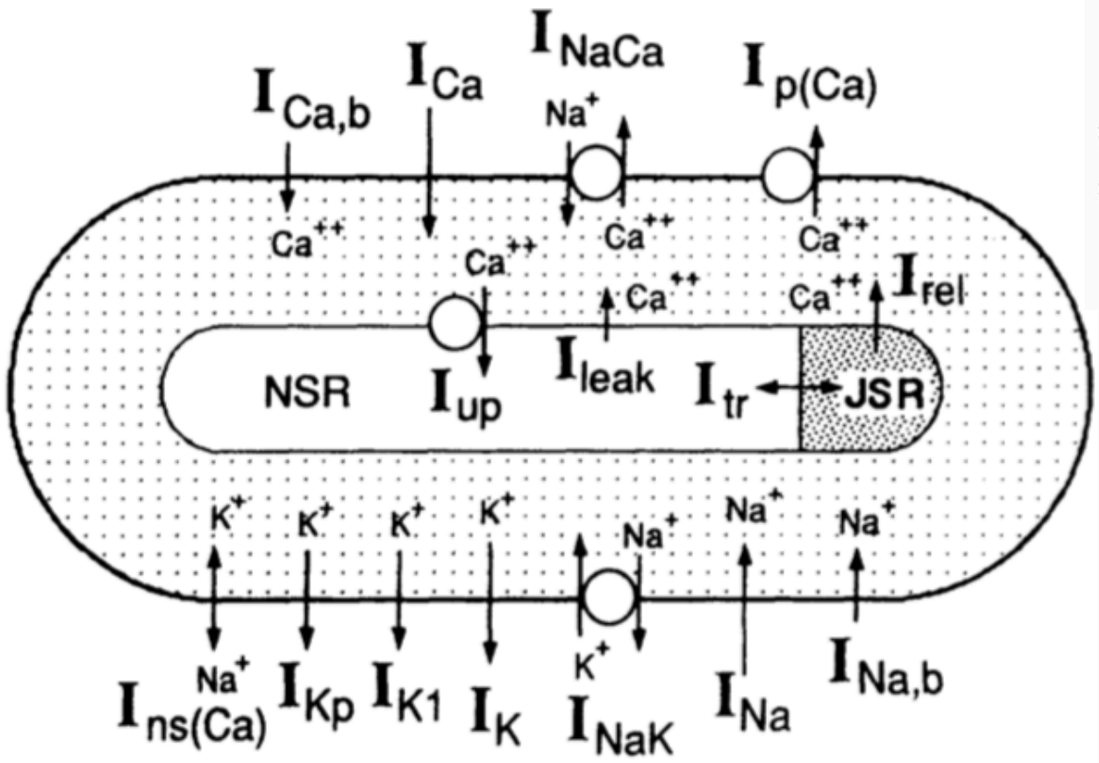


Hodgkin, A. L., & Huxley, A. F. (1952). Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *The Journal of physiology*, *116*(4), 449-472.

Non linear ODE
Conservation laws

Modeling: cardiac electrophysiology

- Cell scale: ionic model



Luo-Rudy model

Luo, C. H., & Rudy, Y. (1991). A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction. Circulation research, 68(6), 1501-1526.

Appendix 1: Formulation of the Model

I. Cell geometry

a. Dimensions: length (L) = 100 μm; radius (r) = 11 μm
b. Cell volume: $V_{cell} = \pi r^2 L = 38 \times 10^{-6}$ μL
c. Geometric membrane area: $A_{Geo} = 2\pi r^2 + 2\pi rL = 0.767 \times 10^{-4}$ cm^2
d. Capacitive membrane area: $A_{Cap} = R_{CG} \cdot A_{Geo} = 1.534 \times 10^{-4}$ cm^2
e. Myoplasm volume: $V_{myo} = V_{cell} \cdot 68\% = 25.84 \times 10^{-6}$ μL
f. Mitochondria volume: $V_{mito} = V_{cell} \cdot 26\% = 9.88 \times 10^{-6}$ μL
g. SR volume: $V_{SR} = V_{cell} \cdot 6\% = 2.28 \times 10^{-6}$ μL
h. NSR volume: $V_{NSR} = V_{cell} \cdot 5.52\% = 2.098 \times 10^{-6}$ μL
i. JSR volume: $V_{JSR} = V_{cell} \cdot 0.48\% = 0.182 \times 10^{-6}$ μL
j. Cleft volume: $V_{cleft} = (V_{cell}/88\%) \cdot 12\% = 5.182 \times 10^{-6}$ μL

II. Standard ionic concentrations

$[K^+]_o = 5.4$ mmol/L; $[K^+]_i = 145$ mmol/L; $[Na^+]_o = 140$ mmol/L; $[Na^+]_i = 10$ mmol/L;
$[Ca^{2+}]_o = 1.8$ mmol/L; and $[Ca^{2+}]_{i,rest} = 0.12$ μmol/L

III. Ionic currents in the sarcolemma

a. Fast sodium current: I_{Na}

$I_{Na} = \bar{G}_{Na} \cdot m^3 \cdot h \cdot j \cdot (V - E_{Na})$;
$E_{Na} = (RT/F) \cdot \ln([Na^+]_o/[Na^+]_i)$; and $\bar{G}_{Na} = 16$ millisiemens/μF.

For $V \geq -40$ mV,

$\alpha_h = \alpha_j = 0.0$; $\beta_h = 1/\left(0.13\{1+\exp[(V+10.66)/-11.1]\}\right)$;
and $\beta_j = 0.3 \cdot \exp(-2.535 \times 10^{-7} V)/\{1+\exp[-0.1(V+32)]\}$.

For $V < -40$ mV,
$\alpha_h = 0.135 \cdot \exp[(80+V)/-6.8]$;
$\beta_h = 3.56 \cdot \exp(0.079V) + 3.1 \times 10^5 \cdot \exp(0.35V)$;
$\alpha_j = \{-1.2714 \times 10^5 \cdot \exp(0.2444V) - 3.474 \times 10^{-5} \cdot \exp(-0.04391V)\} \cdot (V+37.78)/\{1+\exp[0.311 \cdot (V+79.23)]\}$; and
$\beta_j = 0.1212 \cdot \exp(-0.01052V)/\{1+\exp[-0.1378(V+40.14)]\}$.

And, for all range of V,
$\alpha_m = 0.32(V+47.13)/\{1-\exp[-0.1(V+47.13)]\}$;
$\beta_m = 0.08 \cdot \exp(-V/11)$.

b. Currents through the L-type Ca^{2+} channel

$I_{Ca,L} = I_{Ca} + I_{Ca,K} + I_{Ca,Na}$;
$I_{Ca} = d \cdot f \cdot f_{Ca} \cdot I_{Ca}$; $I_{Ca,K} = d \cdot f \cdot f_{Ca} \cdot \bar{I}_{Ca,K}$; and $I_{Ca,Na} = d \cdot f \cdot f_{Ca} \cdot \bar{I}_{Ca,Na}$.

For ion S, including Ca^{2+}, Na^+, and K^+,

$$\bar{I}_S = P_S \cdot z_s^2 \cdot \frac{VF^2}{RT} \cdot \frac{\gamma_{si} \cdot [S]_i \cdot \exp(z_s VF/RT) - \gamma_{so} \cdot [S]_o}{\exp(z_s VF/RT) - 1};$$

$P_{Ca} = 5.4 \times 10^{-4}$ cm/s; $\gamma_{Cai} = 1$; $\gamma_{Cao} = 0.341$;
$P_{Na} = 6.75 \times 10^{-7}$ cm/s; $\gamma_{Nai} = \gamma_{Nao} = 0.75$;
$P_K = 1.93 \times 10^{-7}$ cm/s; $\gamma_{Ki} = \gamma_{Ko} = 0.75$;
$f_{Ca} = 1/[1 + ([Ca^{2+}]_i/K_{m,Ca})^2]$; $K_{m,Ca} = 0.6$ μmol/L;
$d_\infty = 1/\{1+\exp[-(V+10)/6.24]\}$;
$\tau_d = d_\infty \cdot \{1-\exp[-(V+10)/6.24]\}/[0.035 \cdot (V+10)]$;
$f_\infty = 1/\{1+\exp[(V+35.06)/8.6]\} + 0.6/\{1+\exp[(50-V)/20]\}$;

$$\tau_f = 1/\left(0.0197 \cdot \exp\{-[0.0337 \cdot (V+10)]^2\} + 0.02\right);$$

$\alpha_d = d_\infty/\tau_d$; $\beta_d = (1-d_\infty)/\tau_d$; $\alpha_f = f_\infty/\tau_f$; and $\beta_f = (1-f_\infty)/\tau_f$.

c. Time-dependent K^+ current: I_K

$I_K = \bar{G}_K \cdot X_i \cdot X^2 \cdot (V - E_K)$; $P_{Na,K} = 0.01833$;
$E_K = (RT/F) \cdot \ln\{([K^+]_o + P_{Na,K}[Na^+]_o)/([K^+]_i + P_{Na,K}[Na^+]_i)\}$;
$\bar{G}_K = 0.282 \cdot \sqrt{[K^+]_o/5.4}$ millisiemens/μF;
$X_i = 1/\{1+\exp[(V-56.26)/32.1]\}$;
$\alpha_X = 7.19 \times 10^{-5} \cdot (V+30)/\{1-\exp[-0.148 \cdot (V+30)]\}$; and
$\beta_X = 1.31 \times 10^{-4} \cdot (V+30)/\{-1+\exp[0.0687 \cdot (V+30)]\}$.

d. Time-independent K^+ current: I_{K1}

$I_{K1} = \bar{G}_{K1} \cdot K1_\infty \cdot (V - E_{K1})$; $E_{K1} = (RT/F) \cdot \ln([K^+]_o/[K^+]_i)$;
$\bar{G}_{K1} = 0.75 \cdot \sqrt{[K^+]_o/5.4}$ millisiemens/μF;
$\alpha_{K1} = 1.02/\{1+\exp[0.2385 \cdot (V - E_{K1} - 59.215)]\}$; and
$\beta_{K1} = \{0.49124 \cdot \exp[0.08032 \cdot (V - E_{K1} + 5.476)] + \exp[0.06175 \cdot (V - E_{K1} - 594.31)]\}/\{1+\exp[-0.5143 \cdot (V - E_{K1} + 4.753)]\}$

e. Plateau K^+ current: I_{Kp}

$I_{Kp} = \bar{G}_{Kp} \cdot Kp \cdot (V - E_{Kp})$; $\bar{G}_{Kp} = 0.0183$ millisiemens/μF;
$E_{Kp} = E_{K1}$; and $Kp = 1/\{1+\exp[(7.488-V)/5.98]\}$.

f. Na^+-Ca^{2+} exchanger: I_{NaCa}

$$I_{NaCa} = k_{NaCa} \cdot \frac{1}{K_{m,Na}^3 + [Na^+]_o^3} \cdot \frac{1}{K_{m,Ca} + [Ca^{2+}]_o} \cdot \frac{1}{1 + k_{sat} \cdot \exp\left[(\eta - 1) \cdot V \cdot \frac{F}{RT}\right]}$$

$$\cdot \{\exp\left(\eta \cdot V \cdot \frac{F}{RT}\right)[Na^+]_i^3 \cdot [Ca^{2+}]_o - \exp\left[(\eta - 1) \cdot V \cdot \frac{F}{RT}\right][Na^+]_o^3 \cdot [Ca^{2+}]_i\};$$

$k_{NaCa} = 2000$ μA/μF; $K_{m,Na} = 87.5$ mmol/L; $K_{m,Ca} = 1.38$ mmol/L; $k_{sat} = 0.1$; and $\eta = 0.35$.

g. Na^+-K^+ pump: I_{NaK}

$$I_{NaK} = \bar{I}_{NaK} \cdot f_{NaK} \cdot \frac{1}{1 + (K_{m,Na}/[Na^+]_i)^{1.5}} \cdot \frac{[K^+]_o}{[K^+]_o + K_{m,Ko}};$$

$\bar{I}_{NaK} = 1.5$ μA/μF; $K_{m,Nai} = 10$ mmol/L; $K_{m,Ko} = 1.5$ mmol/L;

$$f_{NaK} = \frac{1}{1 + 0.1245 \cdot \exp\left(-0.1 \cdot \frac{VF}{RT}\right) + 0.0365 \cdot \sigma \cdot \exp\left(-\frac{VF}{RT}\right)}; \text{ and}$$

$$\sigma = \frac{1}{7} \cdot \left[\exp\left(\frac{[Na^+]_o}{67.3}\right) - 1\right].$$

h. Nonspecific Ca^{2+}-activated current: $I_{ns(Ca)}$

$$I_{ns,K} = \bar{I}_{ns,K} \cdot \frac{1}{1 + (K_{m,ns(Ca)}/[Ca^{2+}]_i)^3};$$

$$I_{ns,Na} = \bar{I}_{ns,Na} \cdot \frac{1}{1 + (K_{m,ns(Ca)}/[Ca^{2+}]_i)^3};$$

$I_{ns(Ca)} = I_{ns,K} + I_{ns,Na}$;
$P_{ns(Ca)} = 1.75 \cdot 10^{-7}$ cm/s; $K_{m,ns(Ca)} = 1.2$ μmol/L; and

$$E_{ns(Ca)} = \frac{RT}{F} \cdot \ln\frac{[K^+]_o + [Na^+]_o}{[K^+]_i + [Na^+]_i}.$$

($\bar{I}_{ns}$ is computed from P_{ns} using the relation in IIIb of this appendix with the same γ values.)

i. Sarcolemmal Ca^{2+} pump: $I_{p(Ca)}$

$$I_{p(Ca)} = \bar{I}_{p(Ca)} \cdot \frac{[Ca^{2+}]_i}{K_{m,p(Ca)} + [Ca^{2+}]_i};$$

$\bar{I}_{p(Ca)} = 1.15$ μA/μF; $K_{m,p(Ca)} = 0.5$ μmol/L.

j. Ca^{2+} background current: $I_{Ca,b}$

$I_{Ca,b} = \bar{G}_{Ca,b} \cdot (V - E_{Ca,N})$;
$E_{Ca,N} = (RT/2F) \cdot \ln([Ca^{2+}]_o/[Ca^{2+}]_i)$; and $\bar{G}_{Ca,b} = 0.003016$ millisiemens/μF.

k. Na^+ background current: $I_{Na,b}$

$I_{Na,b} = \bar{G}_{Na,b} \cdot (V - E_{Na,N})$; $E_{Na,N} = E_{Na}$; and $\bar{G}_{Na,b} = 0.00141$ millisiemens/μF.

l. Total time-independent current: I_V

$I_V = I_{K1} + I_{Kp} + I_{p(Ca)} + I_{Na,b} + I_{Ca,b} + I_{NaK}$.

IV. Ca^{2+} buffers in the myoplasm

Troponin (TRPN) and calmodulin (CMDN);
buffered $[TRPN] = \overline{[TRPN]} \cdot \{[Ca^{2+}]_i/([Ca^{2+}]_i + K_{m,TRPN})\}$;
buffered $[CMDN] = \overline{[CMDN]} \cdot \{[Ca^{2+}]_i/([Ca^{2+}]_i + K_{m,CMDN})\}$;
$\overline{[TRPN]} = 70$ μmol/L; $\overline{[CMDN]} = 50$ μmol/L; $K_{m,TRPN} = 0.5$ μmol/L; and $K_{m,CMDN} = 2.38$ μmol/L.

V. Ca^{2+} fluxes in the sarcoplasmic reticulum

a. Ca^{2+}-induced Ca^{2+} release of JSR

$I_{rel} = G_{rel} \cdot ([Ca^{2+}]_{JSR} - [Ca^{2+}]_i)$ mmol/L per millisecond

If $\Delta[Ca^{2+}]_{i,2} > \Delta[Ca^{2+}]_{i,th}$ 2 milliseconds after the time of $\dot{V}_{max}$,

$$G_{rel} = \bar{G}_{rel} \cdot \frac{\Delta[Ca^{2+}]_{i,2} - \Delta[Ca^{2+}]_{i,th}}{K_{m,rel} + \Delta[Ca^{2+}]_{i,2} - \Delta[Ca^{2+}]_{i,th}} \cdot (1 - \exp[-t/\tau_{on}]) \cdot \exp[-t/\tau_{off}];$$

$\Delta[Ca^{2+}]_{i,th} = 0.18$ μmol/L; $K_{m,rel} = 0.8$ μmol/L; $\tau_{on} = \tau_{off} = 2$ milliseconds; t=0 at time of CICR;
$\bar{G}_{rel} = 18$ ms^{-1} for voltage clamp simulations; and
$\bar{G}_{rel} = 60$ ms^{-1} for action potential simulations.

If $\Delta[Ca^{2+}]_{i,2} < \Delta[Ca^{2+}]_{i,th}$ at 2 milliseconds, $\bar{G}_{rel} = 0$.

b. Ca^{2+} release of JSR under Ca^{2+}-overload conditions

$I_{rel} = G_{rel} \cdot ([Ca^{2+}]_{JSR} - [Ca^{2+}]_i)$ mmol/L per millisecond

If buffered $[CSQN] \geq [CSQN]_{th}$,
$G_{rel} = \bar{G}_{rel} \cdot (1 - \exp[-t/\tau_{on}]) \cdot \exp[-t/\tau_{off}]$;
$\bar{G}_{rel} = 4$ ms^{-1}; $[CSQN]_{th} = 0.7$ or higher; and $\tau_{on} = \tau_{off} = 2$ milliseconds; and t=0 at time of spontaneous release.

If buffered $[CQSN] < [CQSN]_{th}$, $\bar{G}_{rel} = 0$.

c. Ca^{2+} buffer in JSR and CSQN

Buffered $[CSQN] = \overline{[CSQN]} \cdot \{[Ca^{2+}]_{JSR}/([Ca^{2+}]_{JSR} + K_{m,CSQN})\}$; $\overline{[CSQN]} = 10$ mmol/L; and $K_{m,CSQN} = 0.8$ mmol/L.

d. Ca^{2+} uptake and leakage of NSR: I_{up} and I_{leak}

$I_{up} = I_{up} \cdot [Ca^{2+}]_i/([Ca^{2+}]_i + K_{m,up})$ mmol/L per millisecond; $I_{leak} = K_{leak} \cdot [Ca^{2+}]_{NSR}$ mmol/L per millisecond;
$K_{m,up} = 0.92$ μmol/L; $I_{up} = 0.005$ mmol/L per millisecond;
$K_{leak} = I_{up}/[Ca^{2+}]_{NSR}$ ms^{-1}; and $[Ca^{2+}]_{NSR} = 15$ mmol/L.

e. Translocation of Ca^{2+} ions from NSR to JSR: I_{tr}

$I_{tr} = ([Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR})/\tau_{tr}$ mmol/L per millisecond; $\tau_{tr} = 180$ milliseconds.

Non linear ODE
Conservation laws

Modeling: cardiac electrophysiology

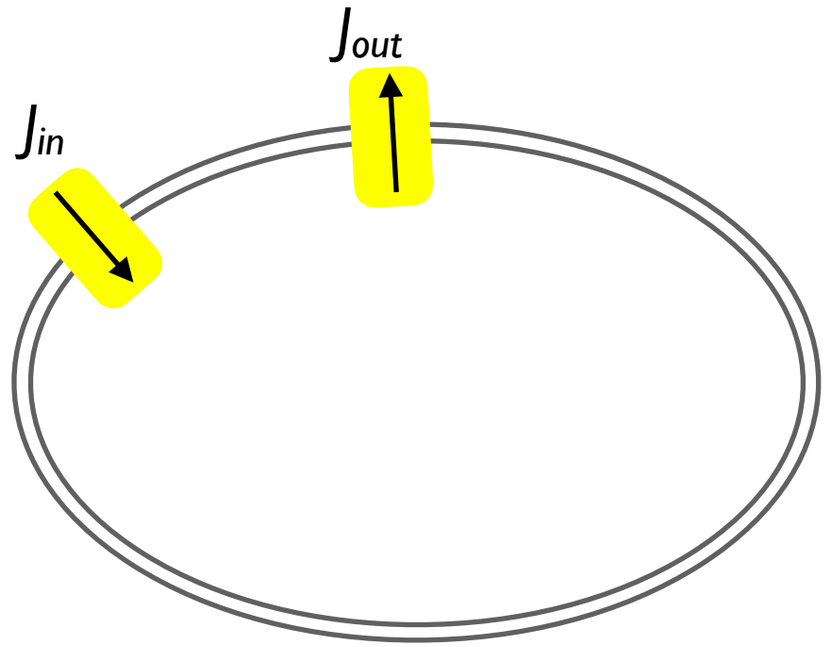
- Cell scale: ionic model

$$I = C_m \dot{V}_m + I_{ion}$$

$$\dot{w} + g(V_m, w) = 0$$

$$I_{ion} = \frac{w}{\tau_{in}} \frac{(V_m - V_{min})^2 (V_m - V_{max})}{V_{max} - V_{min}} - \frac{V_m - V_{min}}{\tau_{out}(V_{max} - V_{min})},$$

$$g(V_m, w) = \begin{cases} \dfrac{w}{\tau_{open}} - \dfrac{1}{\tau_{open}(V_{max} - V_{min})^2} & \text{if } V_m \leq V_{gate}, \\ \dfrac{w}{\tau_{close}} & \text{if } V_m > V_{gate}, \end{cases}$$



Phenomenological model
Example of Mitchell-Schaeffer model (two state variables …)

Non linear ODE
Behaviour laws

Mitchell, C. C., & Schaeffer, D. G. (2003). A two-current model for the dynamics of cardiac membrane. Bulletin of mathematical biology, 65(5), 767-793.

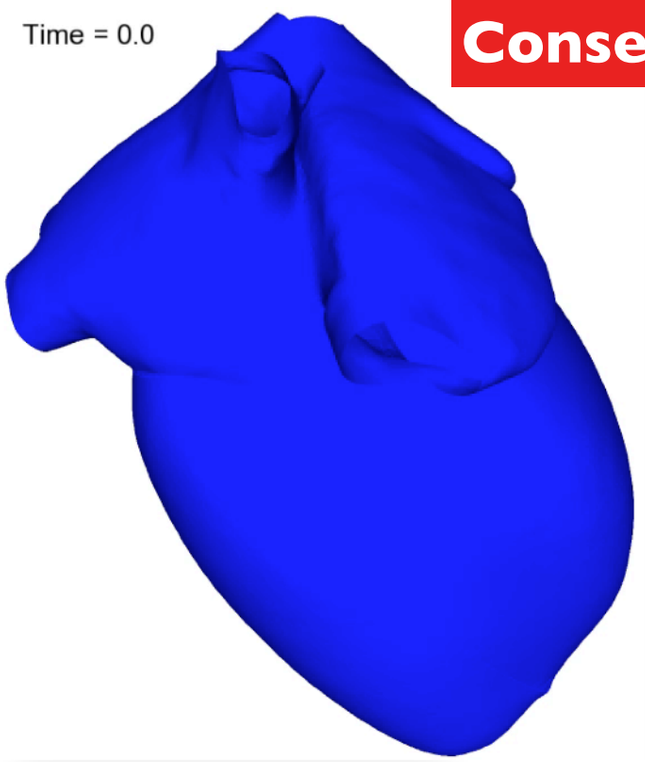
Modeling: cardiac electrophysiology

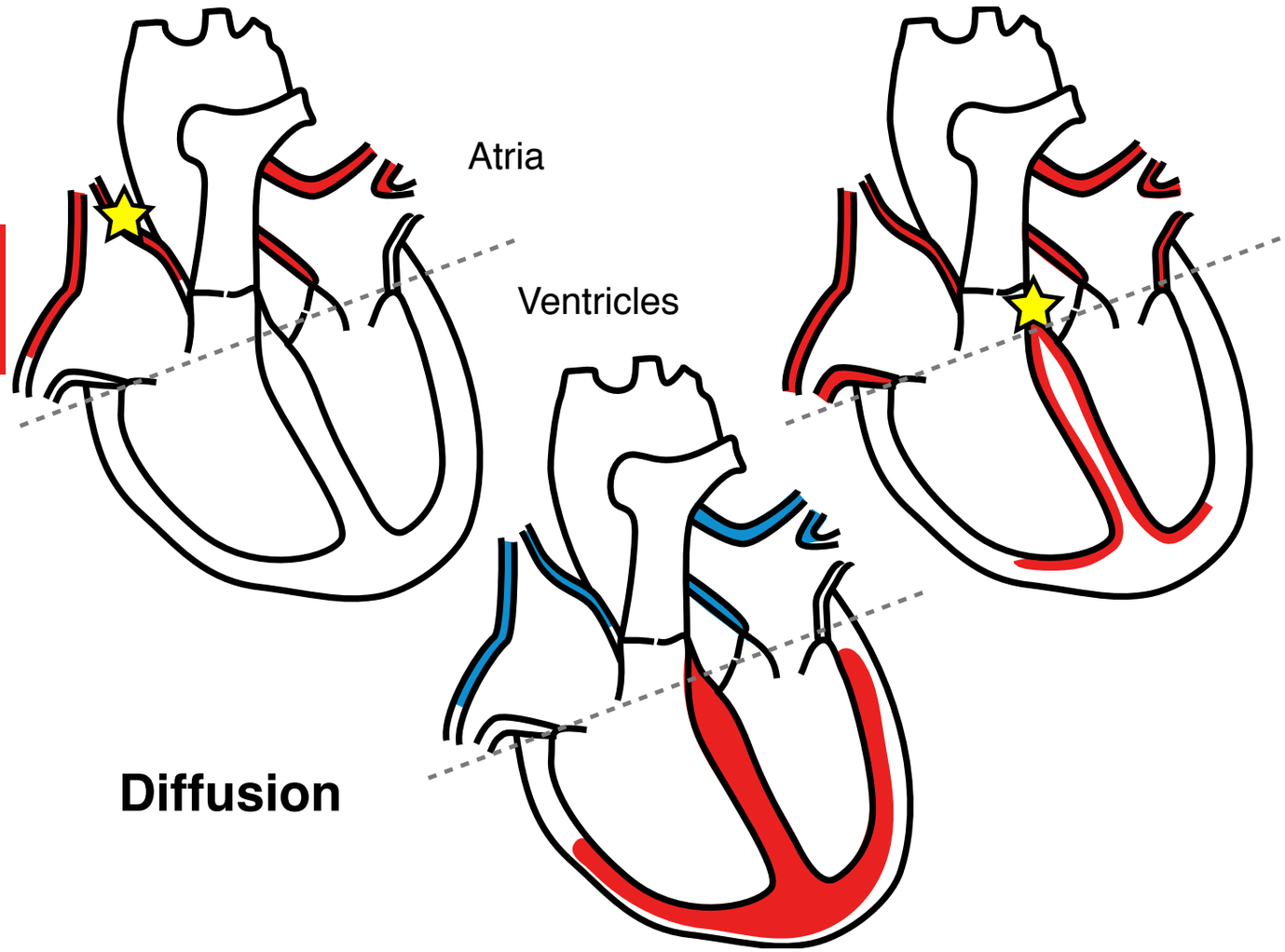
- Heart scale: bidomain model

$$\begin{cases} A_m\left(C_m\dfrac{\partial V_m}{\partial t}+I_{ion}(V_m,\cdots)\right)-\mathrm{div}\left(\vec{\vec{\sigma}}_i\cdot\vec{\nabla}V_m\right) &= \mathrm{div}\left(\vec{\vec{\sigma}}_i\cdot\vec{\nabla}u_e\right)+I_{app}, \\ \mathrm{div}\left(\left(\vec{\vec{\sigma}}_i+\vec{\vec{\sigma}}_e\right)\cdot\vec{\nabla}u_e\right) &= -\mathrm{div}\left(\vec{\vec{\sigma}}_i\cdot\vec{\nabla}V_m\right), \end{cases}$$

L. Tung. A bi-domain model for describing ischemic myocardial d-c potentials. 1978.

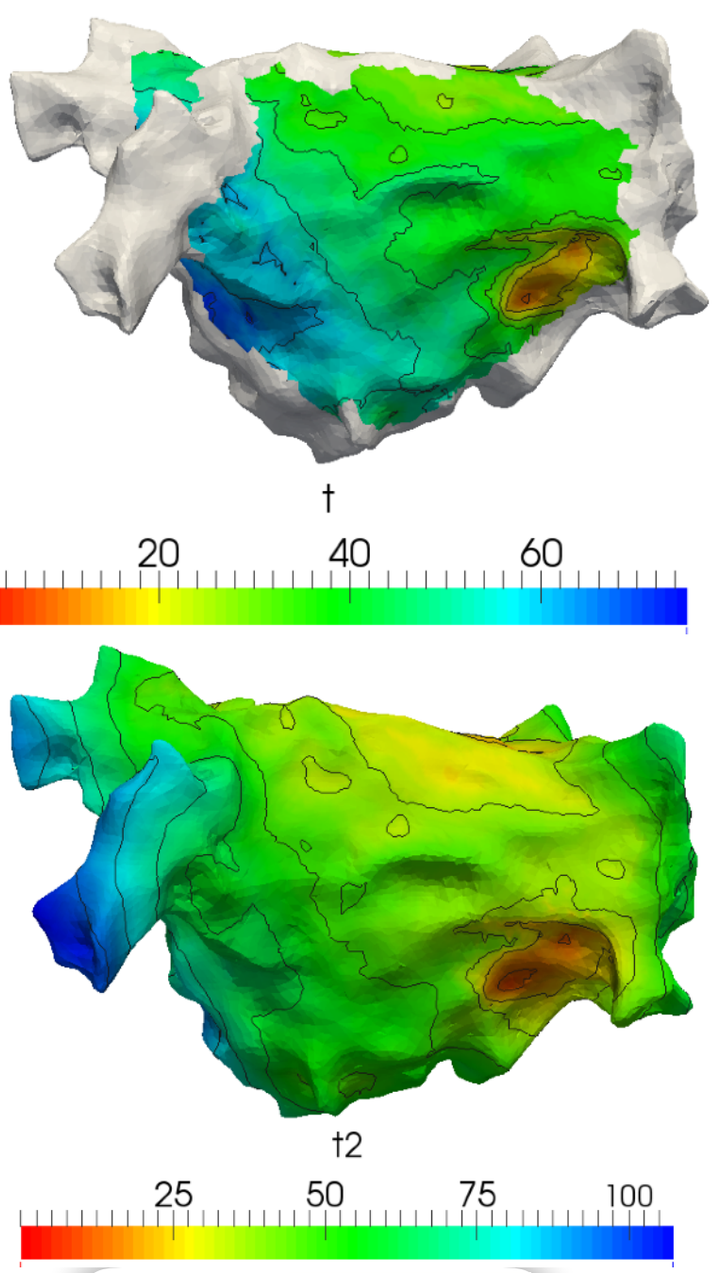
Non linear PDE
Conservation laws

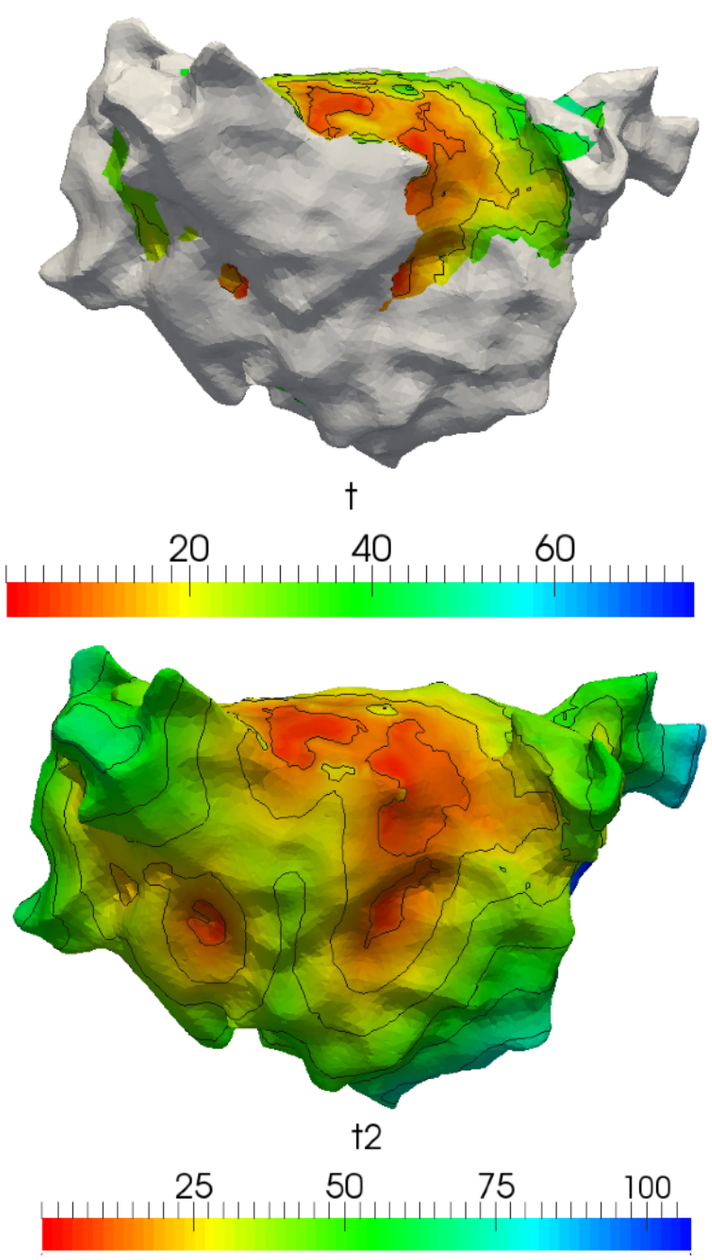




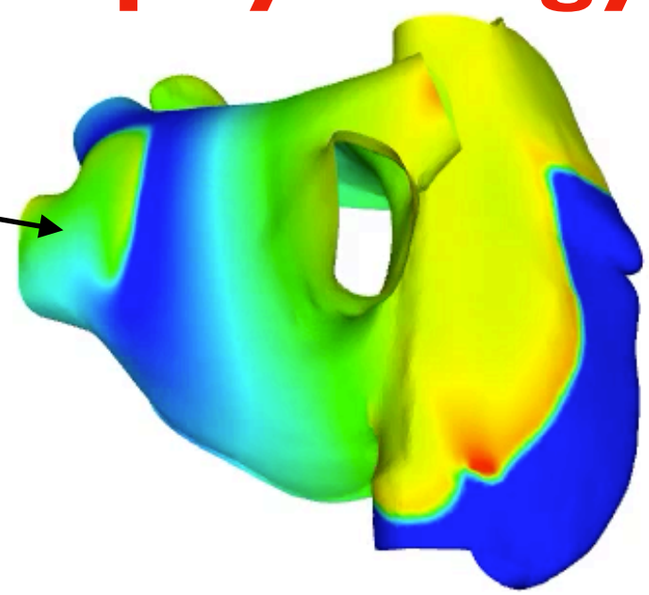
Clinical question: cardiac electrophysiology

- One example: Atrial fibrillation





Pathological area



Real data (Lyric institute)

Left atrium
Incomplete spatial data

A. Collin, D. Chapelle, P. Moireau. A Luenberger observer for reaction-diffusion models with front position data. Journal of Computational Physics, Elsevier, 2015

The strategy allows to reconstruct the whole signal and help to determine the pathological areas

Modeling: cardiac electrophysiology

Linear PDE
Conservation laws

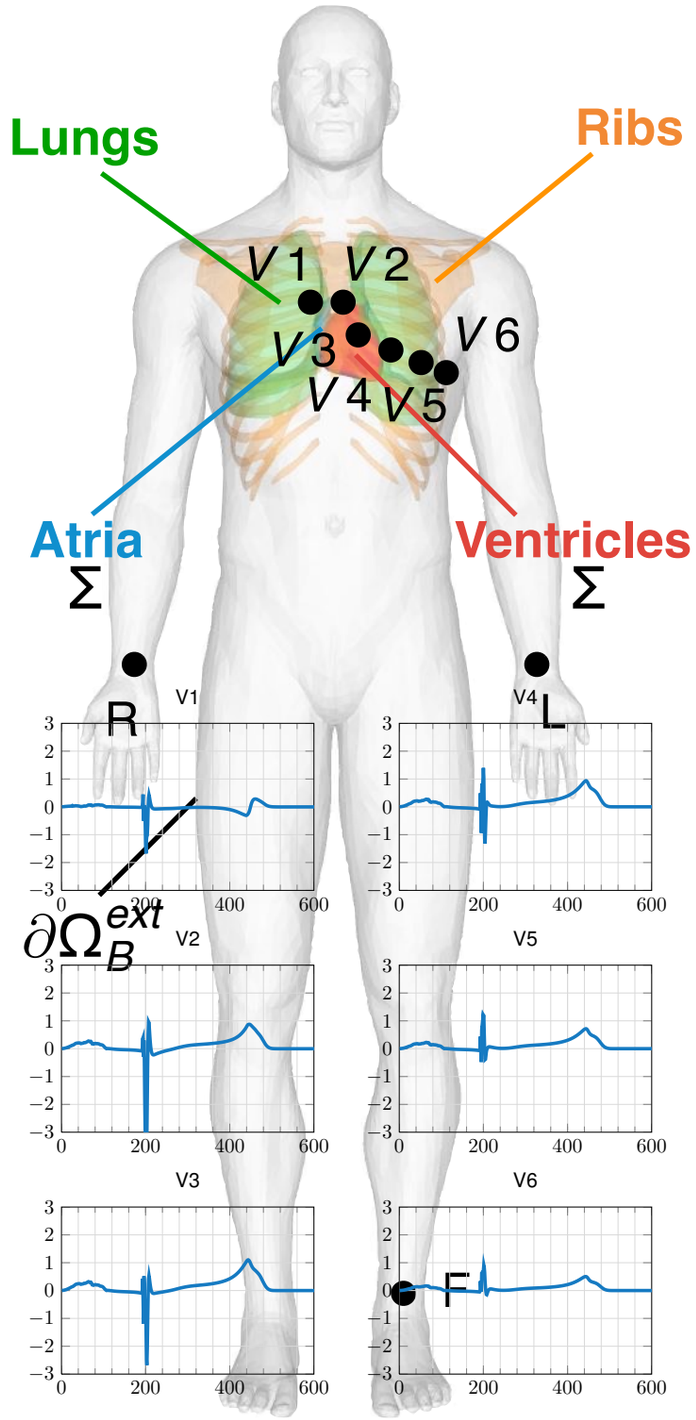
- Electrocardiograms

$$-\operatorname{div}(\sigma_T \vec{\nabla} u_T) = 0, \quad \Omega_B$$ — Body diffusion

$$R_p(\sigma_T \vec{\nabla} u_T) \cdot \vec{n} + u_T = u_e, \partial\Omega_B^{heart}$$

$$\sigma_T \vec{\nabla} u_T \cdot \vec{n} = 0, \ \partial\Omega_B^{ext}$$ — Body = Isolated domain

Coupling conditions between the heart and the body
Weak coupling



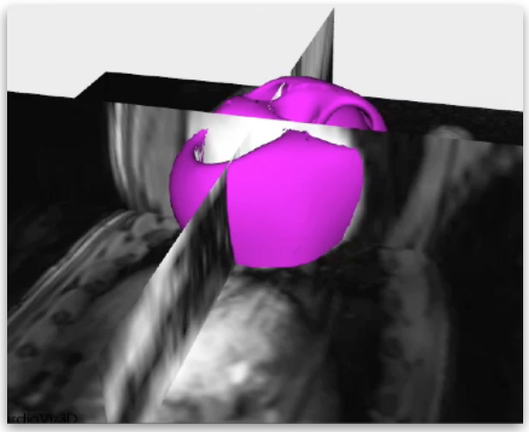
Recording of the potential

Measure the difference of potential at multiple locations on the body surface

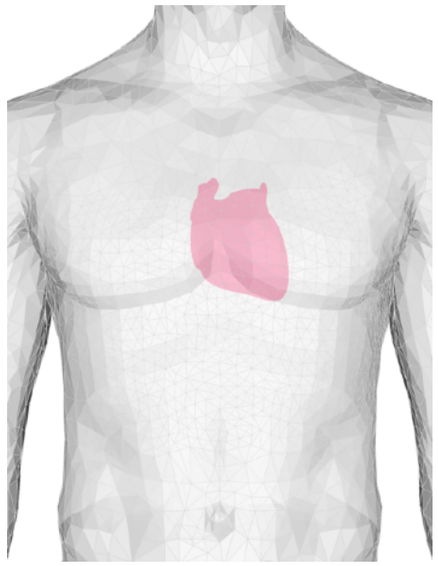
$$I = u_T(L) - u_T(R) \qquad V1 = u_T(V_1) - u_w$$
$$II = u_T(F) - u_T(R) \qquad V2 = u_T(V_2) - u_w$$
$$III = u_T(F) - u_T(L) \qquad V3 = u_T(V_3) - u_w$$
$$aVR = 1.5(u_T(R) - u_w) \qquad V4 = u_T(V_4) - u_w$$
$$aVL = 1.5(u_T(L) - u_w) \qquad V5 = u_T(V_5) - u_w$$
$$aVF = 1.5(u_T(F) - u_w) \qquad V6 = u_T(V_6) - u_w$$

Schenone, E., Collin, A., & Gerbeau, J. F. (2016). Numerical simulation of electrocardiograms for full cardiac cycles in healthy and pathological conditions. IJNMBE, 32(5), e02744.

Clinical question: cardiac electrophysiology



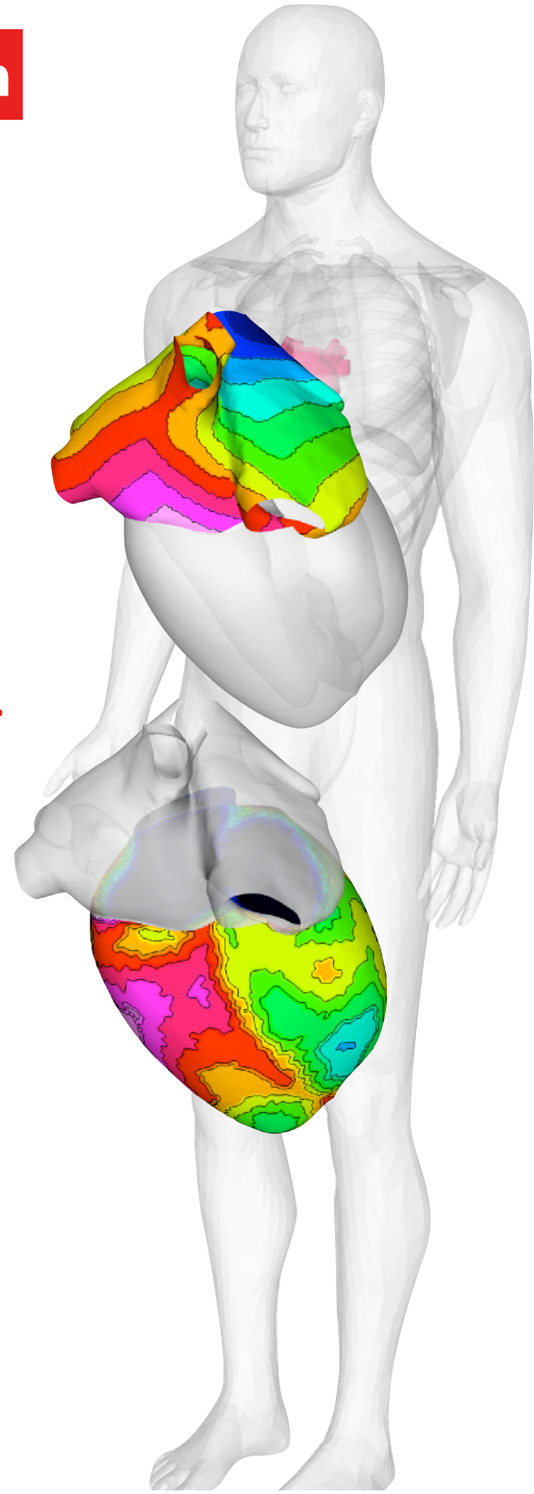
Images (CT, MRI)

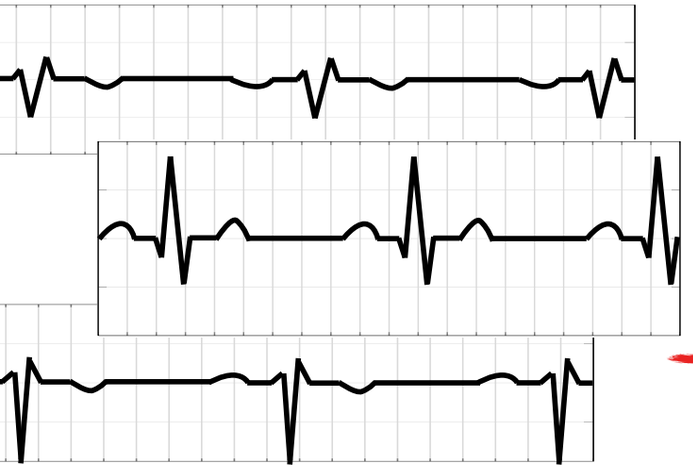


Heart and torso geometries

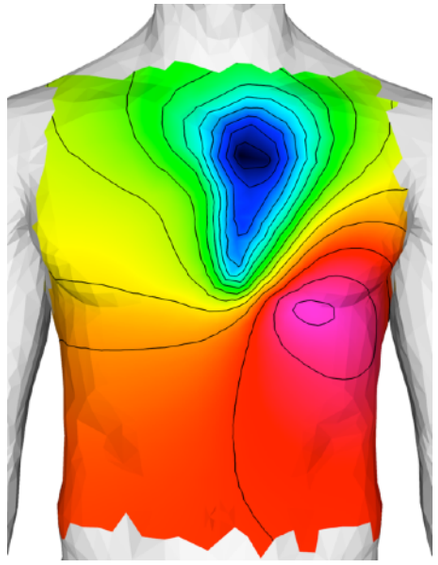
See Friday afternoon

Inverse problem





Electrodes vest (multiple surface ECG recordings)



Body surface potentials

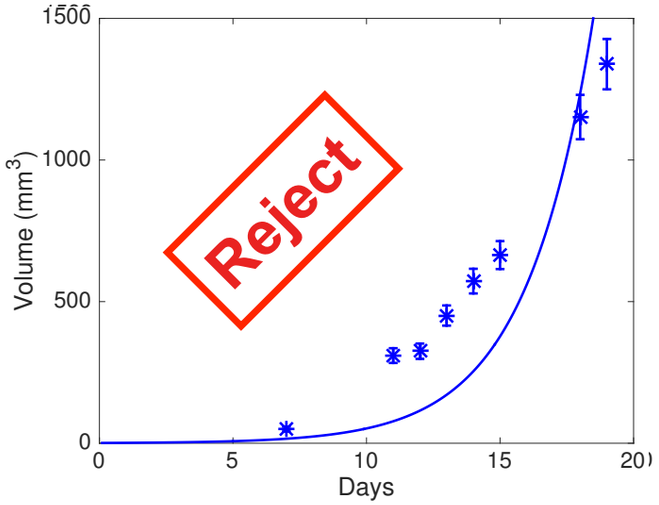
Modeling: tumor growth

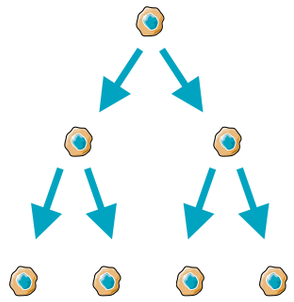
Benzekry, S., Lamont, C., Beheshti, A., Tracz, A., Ebos, J. M., Hlatky, L., & Hahnfeldt, P. (2014). Classical mathematical models for description and prediction of experimental tumor growth. PLoS computational biology, 10(8), e1003800.

- No spatial aspects: volume model …
- What are minimal biological processes able to recover the kinetics of (experimental) tumor growth?

Non linear ODE Behaviour laws

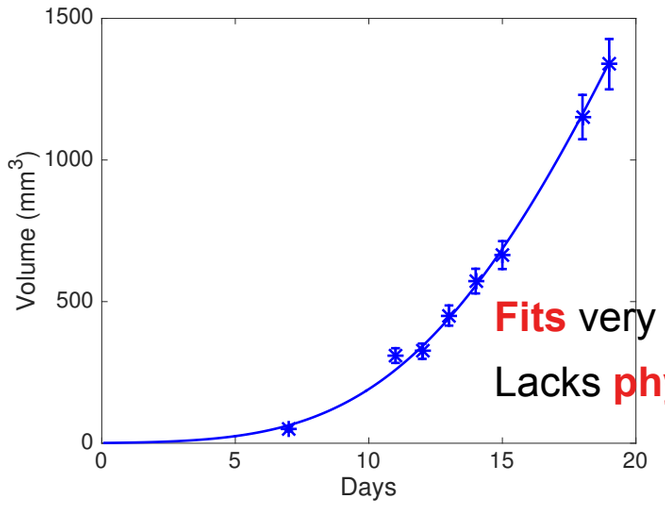
Exponential





$$\frac{dV}{dt} = aV$$

Gompertz

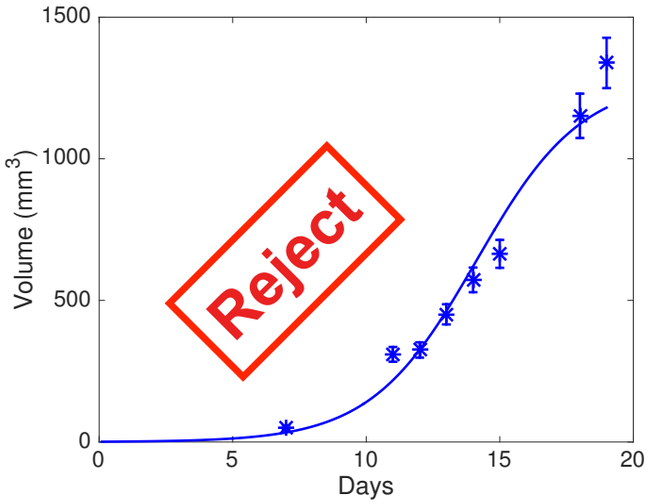


$$\frac{dV}{dt} = \alpha e^{-\beta t} V$$

Fits very well

Lacks **physiological** interpretation

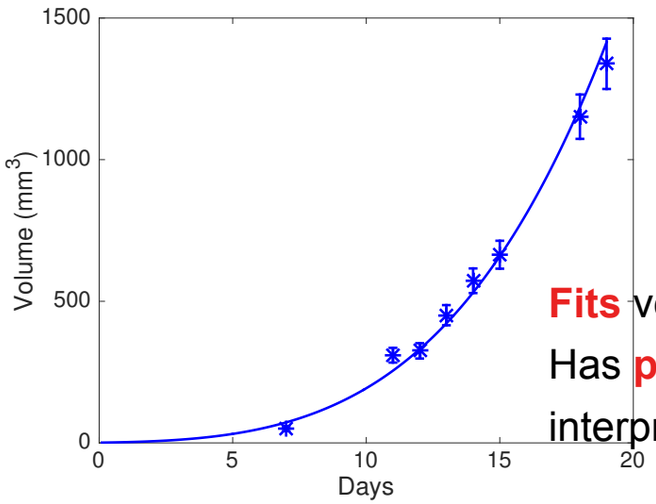
Logistic



Competition

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$$

Power law



$$\frac{dV}{dt} = \alpha V^{\gamma}$$

Fits very well

Has **physiological** interpretation

Modeling: tumor growth

P - tumor cells

S - healthy cells

$P + S = 1$

- Gompertz like model for tumour cells P

$$\partial_t P + \nabla \cdot (v P) = M P,$$

where M is the vasculature

$$\partial_t M = -\alpha M P,$$

with α the decreasing rate of M.

- Outside the tumour

$$\partial_t S + \nabla \cdot (v S) = 0.$$

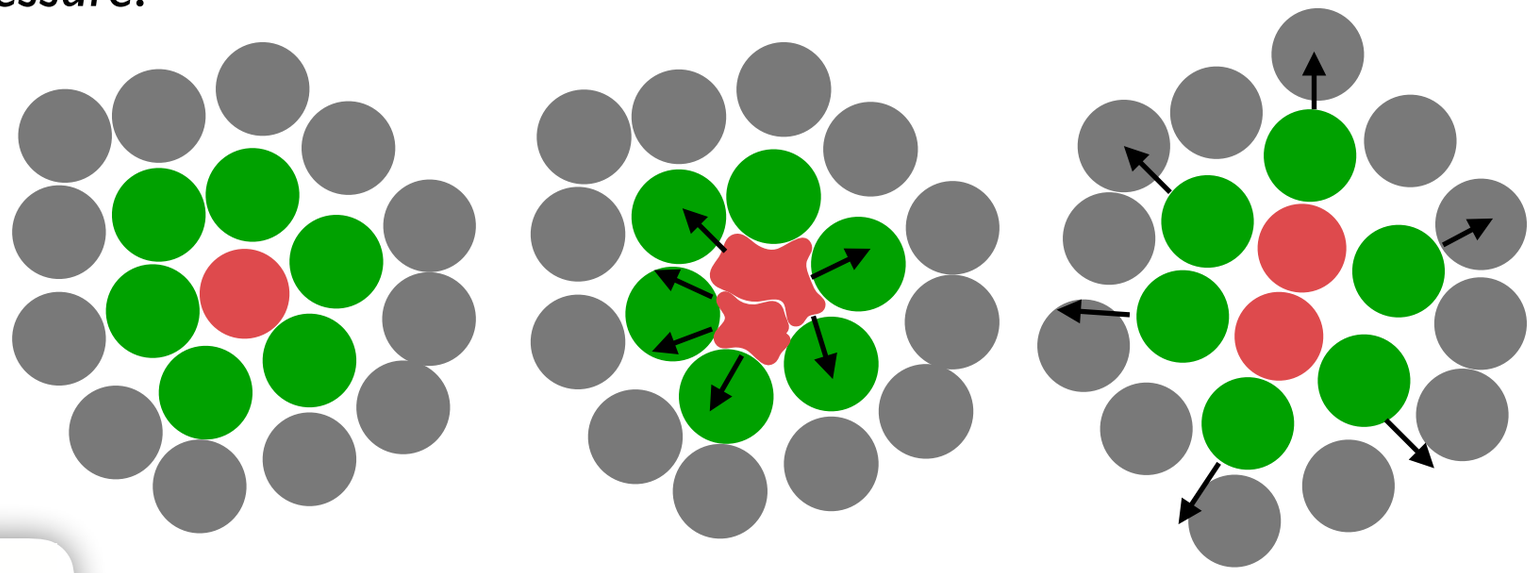
$$\nabla \cdot v = M P$$

- Darcy law representing the cell density velocity

$$v = -\nabla \pi,$$

with π the *pressure*.

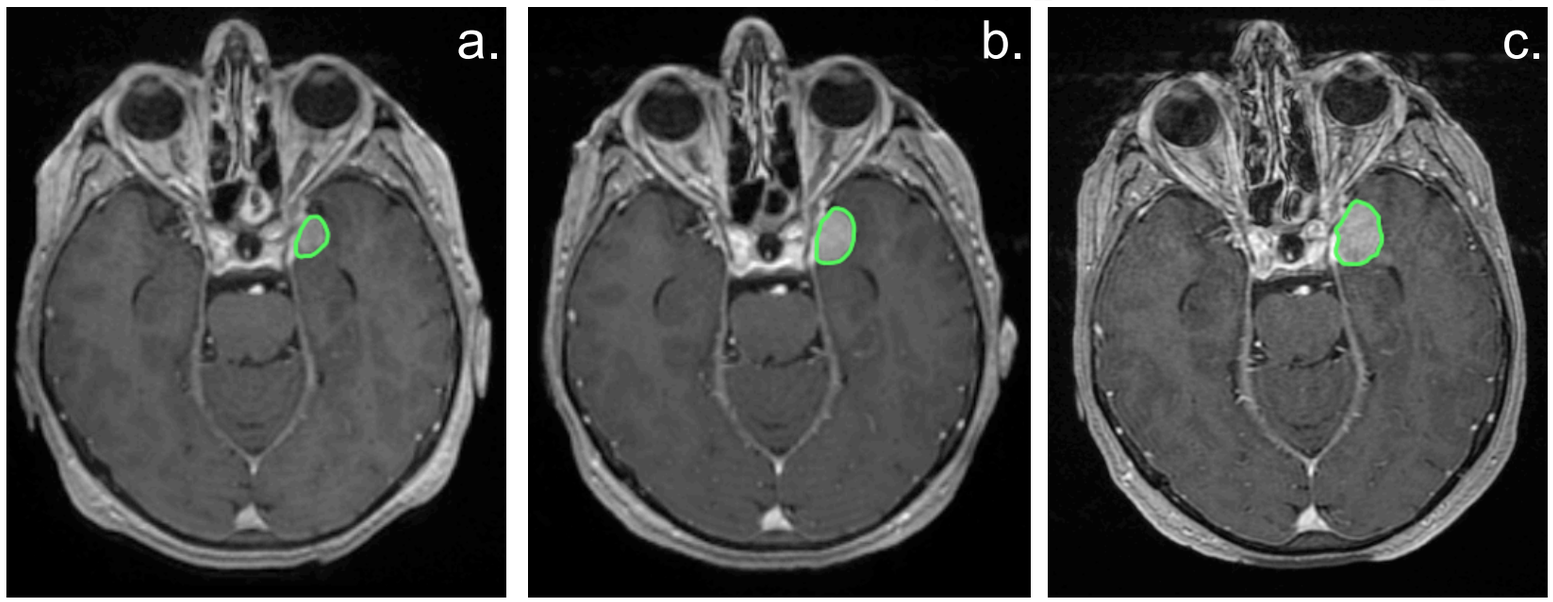
Non linear PDE
Behaviour law
(physiological interpretation)



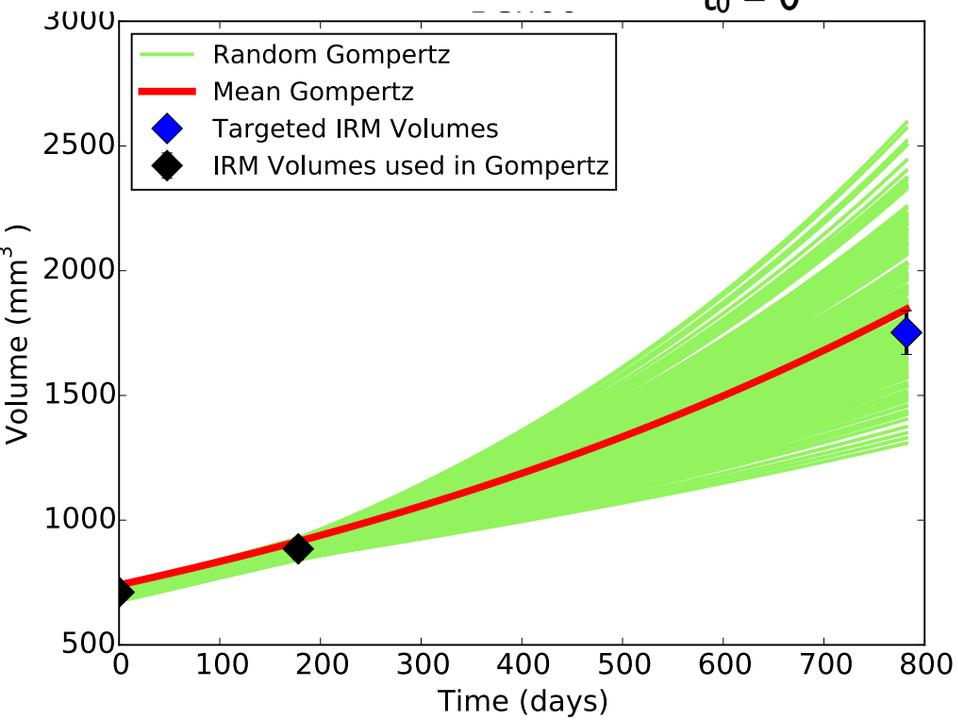
Clinical question: Tumor growth

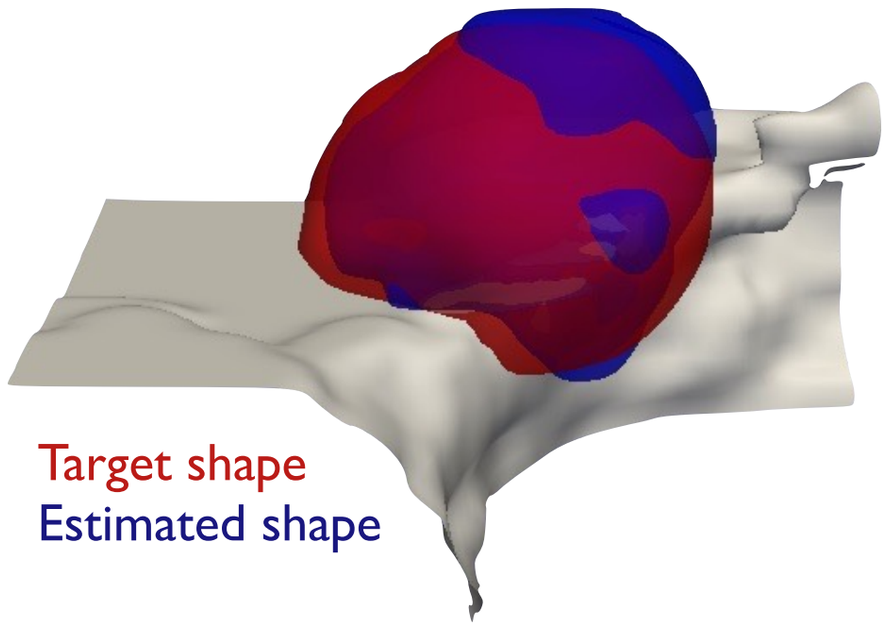
- Predict the volume and the shape of the tumor using the first exams. Meningioma example.

CHU Bordeaux - MRI T1 (with gadolinium contrast agent)



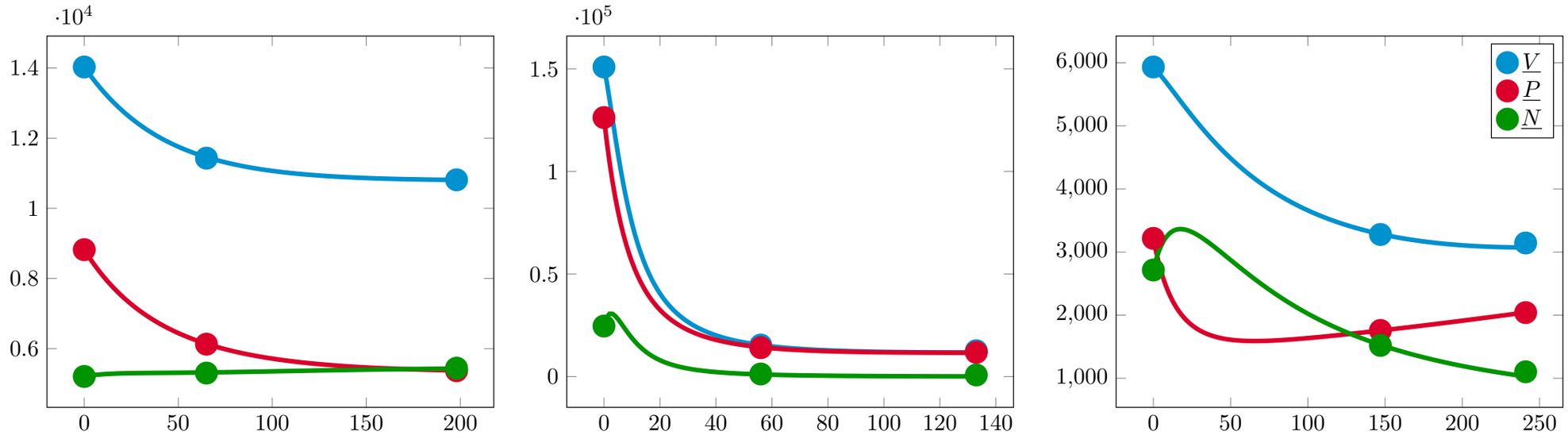
$t_0 = 0$ $t_1 = 169$ days $t_2 = 330$ days





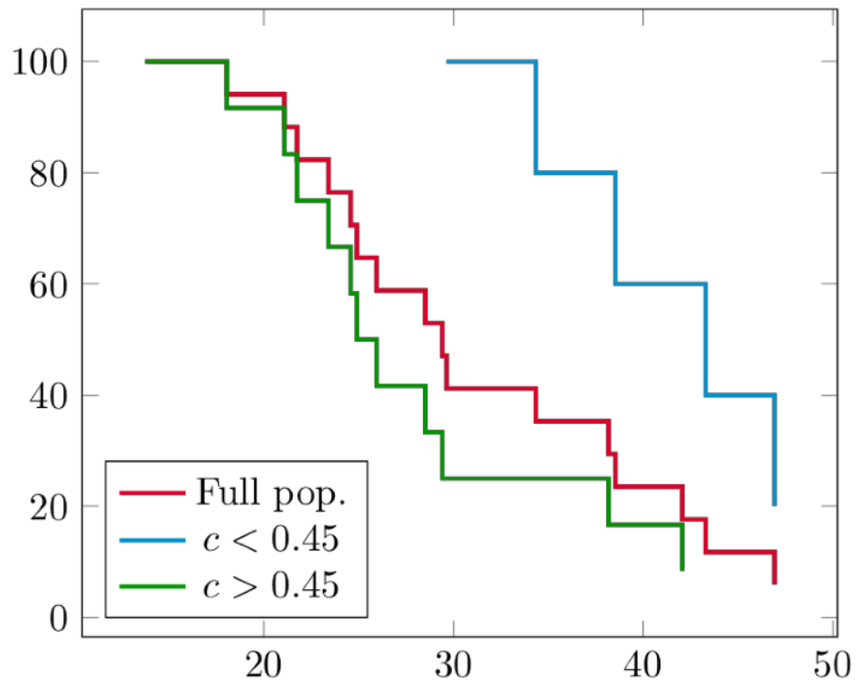
Clinical question: Tumor growth

- Can we predict the relapse using the treatment response? Lung cancer (with EGFR mutation) example.



Time evolution of the densities of proliferative (red) and necrotic (green) cells for 3 patients with the time evolution of the volume (in blue).

hazard rate = 0.2571
[0.0889, 0.7431]
p-value = 0.025



Numerical resolution

Numerical resolution

- Well posed problem: existence and uniqueness of a solution

- Why?
  - Allows to better understand the problem
  - Compatibility with initial condition ; boundary conditions ; source term …

- How?
  - Mathematical theorems (Cauchy-Lipschitz for ODE ; Lax Milgram for PDE for instance)
  - In most cases, the unique solution is not explicit …

★ **Numerical approximation of the solutions …**

Numerical resolution - ODEs

- First-order differential equation

$$\begin{cases} y'(t) &= f(t, y(t)) \\ y(t_0) &= y_0 \end{cases}$$

- Euler method

$$y'(t) = \frac{y(t+h) - y(t)}{h} + O(h) \quad \textit{finite difference approximation}$$

$$y(t+h) = y(t) + h\,y'(t) + O(h^2) = y(t) + h\,f(t, y(t)) + O(h^2)$$

- Let h a step size, we construct the sequence $t_0, t_1 = t_0 + h, t_2 = t_0 + 2h, \ldots$
- We denote by y_n a numerical estimate of the exact solution $y(t_n)$.
- *Euler and backward euler methods*

$$y_{n+1} = y_n + h\,f(t_n, y_n) \qquad y_{n+1} = y_n + h\,f(t_{n+1}, y_{n+1}) \qquad \textbf{+ ...}$$

- A method converges if

$$\lim_{h \to 0} \max_{n=0,\cdots,N} \|y_n - y(t_n)\| = 0$$

- The method has order p if

$$\|y_n - y(t_n)\| = O(h^{p+1})$$

- Euler and backward Euler method have order 1 … Can we do better?

Numerical resolution - ODEs

- *Runge-Kutta methods*
  - Introduction of intermediate steps

$$t_{n,i} = t_n + c_i\, h,\ \ c_i \in [0, 1]$$

  - Exact solution of the problem

$$y(t_{n,i}) = y(t_n) + h \int_0^{c_i} f(t_n + u\, h, y(t_n + u\, h))du$$

$$y(t_{n+1}) = y(t_n) + h \int_0^{1} f(t_n + u\, h, y(t_n + u\, h))du$$

  - Quadrature rules

$$\int_0^{c_i} g(u)du = \sum_{k=1}^{i-1} a_{i,k} g(c_k) + O(h^{i-1}),\ \int_0^{1} g(u)du = \sum_{k=1}^{q} b_k g(c_k) + O(h^q)$$

- Runge-Kutta methods of order q write

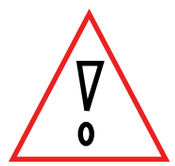
$$\forall i \in 1, \cdots q, \begin{cases} t_{n,i} & = & t_n + c_i\, h \\ y_{n,i} & = & y_h + h \sum_{k=1}^{i-1} a_{i,k} p_{n,k} \\ p_{n,i} & = & f(t_{n,i}, y_{n,i}) \end{cases}$$

$$y_{n+1} = y_n + h \sum_{k=1}^{q} b_k p_{n,k}$$

Numerical resolution - ODEs

- *Linear multistep methods (explicit and implicit methods)*
  - ~~Introduction of intermediate steps~~ Use previous steps

$$y_{n+1} = \sum_{i=0}^{q} \alpha_i y_{n-i} + h \sum_{i=0}^{q} \beta_i f_{n-i}$$



Initial conditions!

  - The method has order p if

$$y_{n+1} = \sum_{i=0}^{m-1} \alpha_i y_{n-i} + h \sum_{i=-1}^{m-1} \beta_i f(t_{n-i}, y_{n-i})$$

$$\sum_{i=0}^{m-1} a_i (-i)^k + k \sum_{i=-1}^{m-1} b_i (-i)^{k-1} = 1$$

- Difference between Runge-Kutta and linear multistep methods

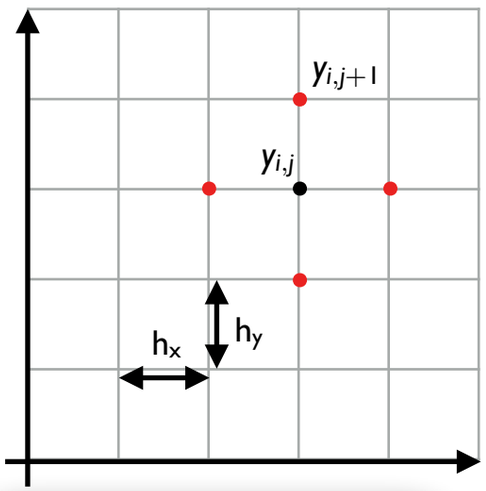
Computational time ⟷ Memory (space complexity)

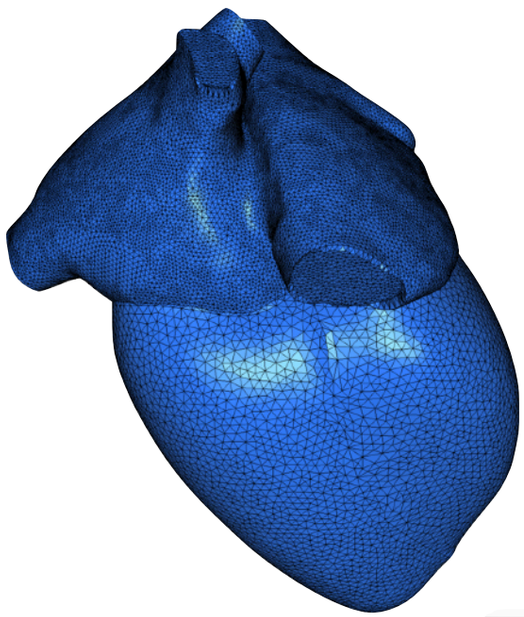
Evaluations of f — *Save* f_{n-i}

Numerical resolution - PDEs

- And for PDEs? Objective: Convert a PDE into a system of equations, which can then be solved by matrix algebra techniques
- Most classical methods: values are calculated at discrete places on a meshed geometry.
  - **Finite difference method.** Finite difference approximates the spatial derivatives. Limited to structured geometry.
  - **Finite element method.** Subdivision of a large system into smaller, simpler parts that are called finite elements. Based on variational methods (divergence theorem).
  - **Finite volume method.** Volume integrals that contain a divergence term are converted to surface integrals, using the divergence theorem. These terms are then evaluated as fluxes at the surfaces of each finite volume. Conservative method (flux entering a given volume is identical to that leaving the adjacent volume).
- After space and time discretizations, the problem can be rewritten as

$$Ax = b \text{ (linear) or } F(x) = 0 \text{ (non linear)}, \quad x \in \mathbb{R}^n$$





$$\begin{cases} \int_\Omega A_m \left(C_m \frac{\partial V_m}{\partial t} + I_{ion}(V_m, \cdots) \right) \tilde{v}_1 + \int_\Omega (\vec{\bar{\sigma}}_i \cdot \vec{\nabla} V_m) \cdot \vec{\nabla} \tilde{v}_1 + (\vec{\bar{\sigma}}_i \cdot \vec{\nabla} u_e) \cdot \vec{\nabla} \tilde{v}_1 = \int_\Omega I_{app} \tilde{v}_1, \\ \int_\Omega ((\vec{\bar{\sigma}}_i + \vec{\bar{\sigma}}_e) \cdot \vec{\nabla} u_e) \cdot \vec{\nabla} \tilde{v}_2 + \int_\Omega (\vec{\bar{\sigma}}_i \cdot \vec{\nabla} V_m) \cdot \vec{\nabla} \tilde{v}_2 = 0, \end{cases}$$

Numerical resolution - PDEs

- Linear systems:
  - Direct solvers (find the exact solution)

Solve Ax = b

    - Gauss (*LU* decomposition with pivoting)

$A = LU$, L lower triangular matrix, U upper triangular matrix

    - Cholesky (hermitian positive definite matrix)

$A = LL^*$, L lower triangular matrix

    - QR decomposition.

$A = QR$, Q orthogonal matrix, R upper triangular matrix

  - Iterative solvers (approximate the solution, for big systems for instance)

$A = M\text{-}N$ with M inversible and very easy to inverse

$$x_{k+1} = M^{-1}Nx_k + M^{-1}b$$

    - Jacobi (for diagonally dominant matrix)

$A = D\text{-}R$ with D diagonal of A

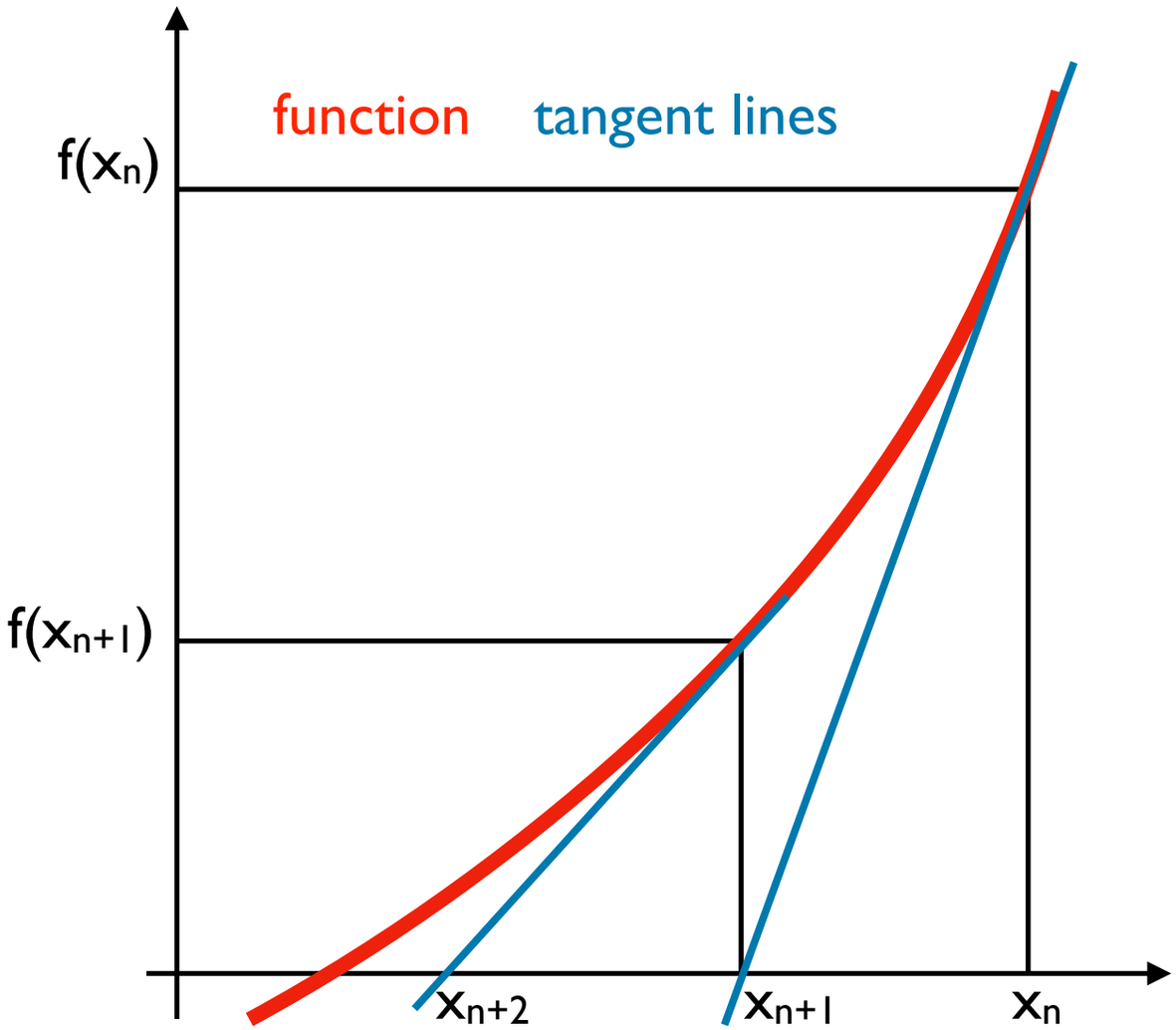
    - Gauss-Siedel

$A = L+R$, L lower triangular component and R strictly upper triangular component

Numerical resolution - PDEs

- Non linear systems (also used for implicit ODE time schemes):
  - Newton-Raphson method

Solve F(x) = 0



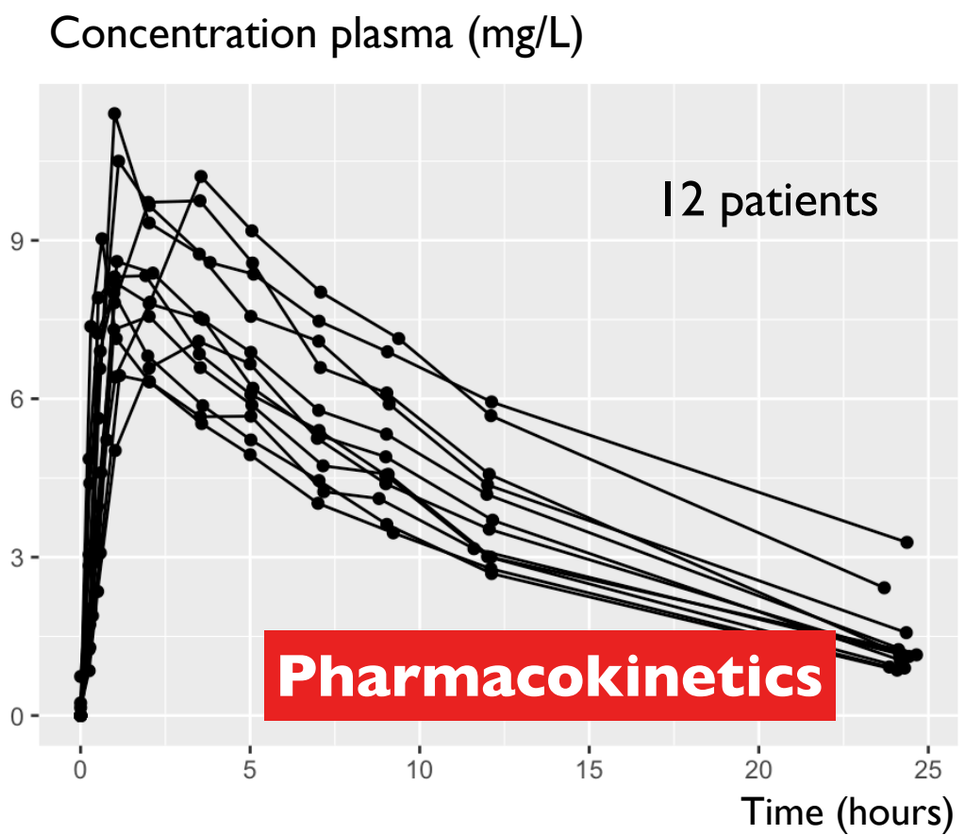
The formula for converging on the root can be easily derived. Suppose we have some current approximation x_n. Then we can derive the formula for a better approximation, x_{n+1} by referring to the diagram on the left. The equation of the tangent line to the curve y=F(x) at the point $x = x_n$ is $y = f'(x_n)(x-x_n) + f(x_n)$. The x-intercept of this line is then used as the next approximation to the root x_{n+1}

- Alternative methods are available in the litterature (depending of the properties of F)

Patient-specific simulation

Patient-specific simulation

- 12 patients *versus* 1 model



$$\begin{cases} \dot{A}_{GI} &= -k_a A_{GI} \\ \dot{U}_P &= \frac{k_a}{V_0} A_{GI} - k_e U_P \end{cases}$$

A_{GI} Dose in Gastro-intertinal compartment (mg)

U_P Concentration Plasma compartment (mg/L)

k_a Drug absorption rate (h^{-1})

k_e Drug elimination rate (h^{-1})

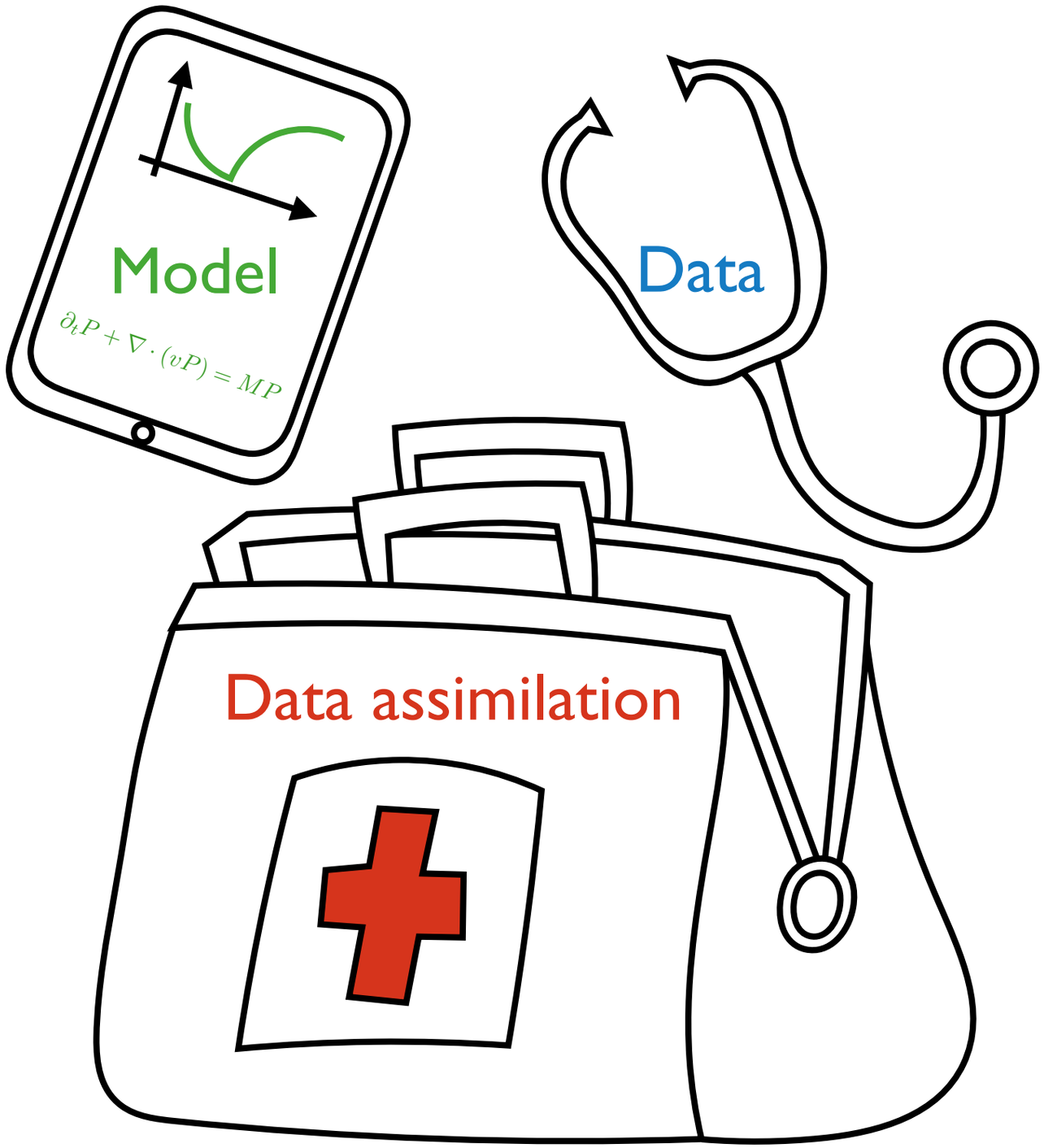
V_0 Volume of distribution (L)

- **Inverse problem**: recover the parameters and/or the initial conditions which have produced some observations

Patient-specific simulation

Model

State u
(ODE or PDE unknown)
Parameters
Uncertainties on the **parameters**, on the **initial condition** …



Data

Partial in time/space
Noisy
Comparison with the state of the model can be difficult

Patient-specific simulation

Model

State u
(ODE or PDE unknown)
Parameters
Uncertainties on the parameters,
on the initial condition …

$$\begin{cases} \dot{u}(t) &= A(u, \theta, t) \\ u(0) &= u_\diamond + \zeta^u \\ \theta(0) &= \theta_\diamond + \zeta^\theta \end{cases} \quad (u_\diamond, \theta_\diamond) \text{, } a \text{ } priori \quad (\zeta^u, \zeta^\theta) \text{, unknown parts}$$

Observations z

Data

Partial in time/space
Noisy
Comparison with the state of the model can be difficult

Find ζ which minimizes the discrepancy

$$z - C(\bar{u}_{|\zeta})$$

(where C is the observation operator)

under the constraint of the model dynamics

$$\begin{cases} \dot{\bar{u}}_{|\zeta}(t) &= A(\bar{u}_{|\zeta}, \theta_\diamond + \zeta^\theta, t) \\ \bar{u}_{|\zeta}(0) &= u_\diamond + \zeta^u \end{cases}$$

with $\zeta = (\zeta^\theta, \zeta^u)$

We can also include error in the dynamical system.

Data assimilation

Strategies for coupling the informations

Many strategies are available with many formalisms as you will in next days :)
But in every cases there are:

- a dynamical model (linear or not)
- an observation model (linear or not) which leads to a discrepancy
- a functional to minimize (or maximize)
- an optimization algorithm