Simulation of the effect of the drug diltiazem on the bioelectric activity of the heart

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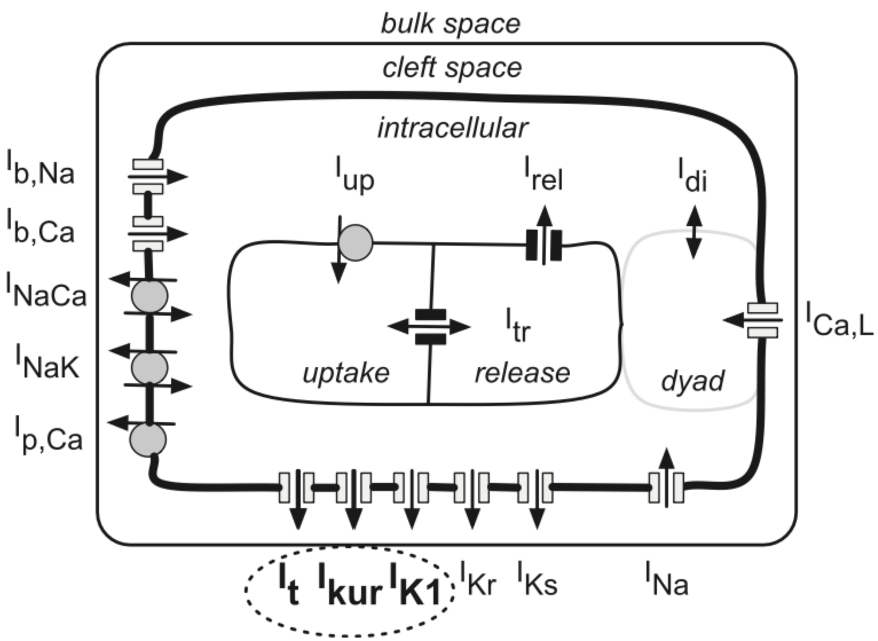
Introduction

Model of an isolated human cardiomyocyte:

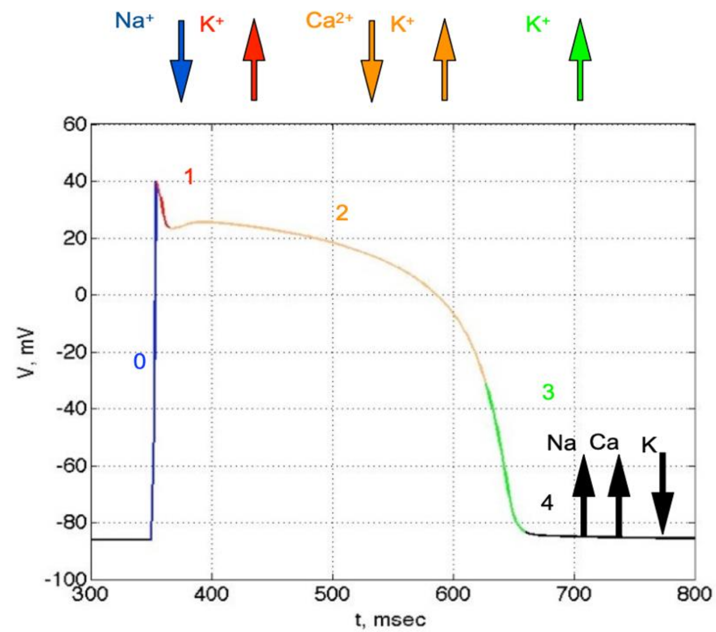


Instantaneous conductance of each channel:

$$G_k = N_k * \sigma_k * f_k$$

Also: $I_k = G_k * (V_m - E_k)$

Action Potential (AP): general waveform



Phase 0: depolarization

Phase 1: early repolarization

Phase 2: plateau

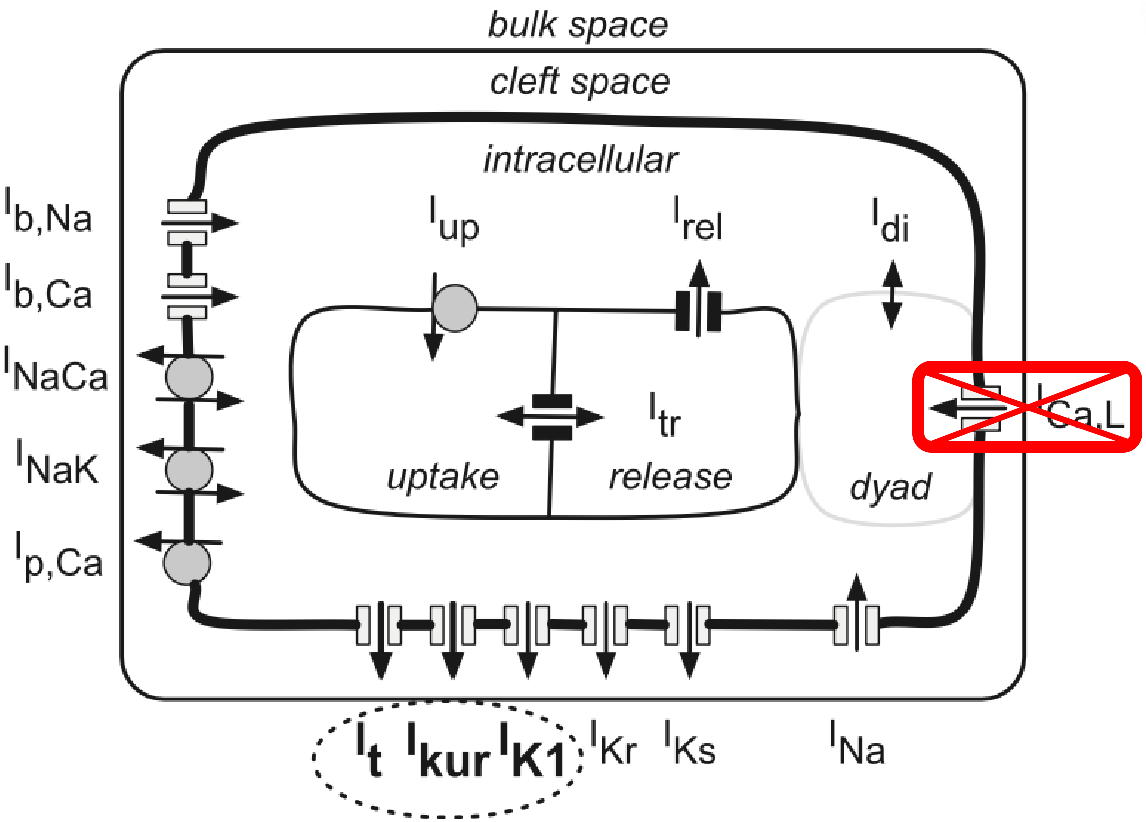
Phase 3: late repolarization

Phase 4: resting potential

Objectives

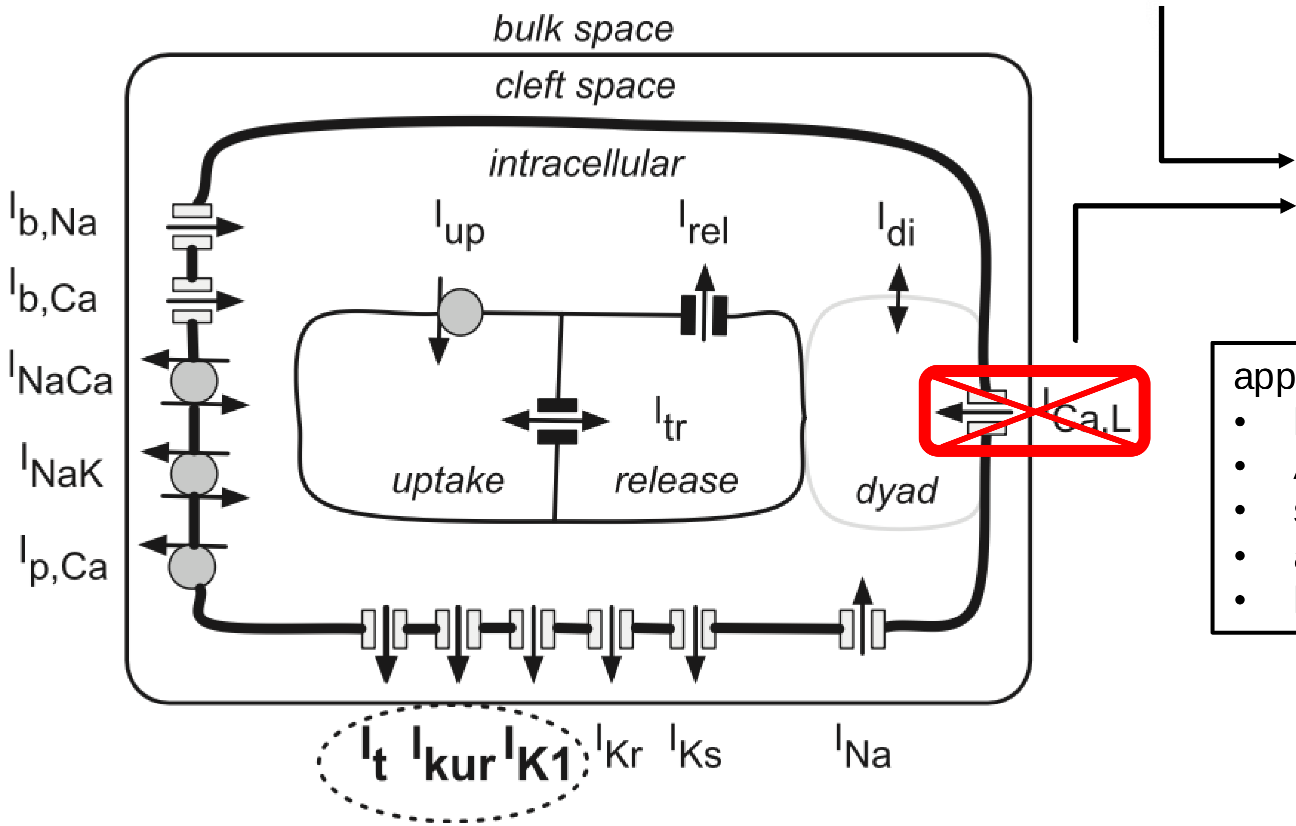
Effects of **diltiazem** on atrial cardiomyocyte:

blockage of **L-type calcium** channels



Objectives

Effects of **diltiazem** on atrial cardiomyocyte:
blockage of **L-type calcium** channels

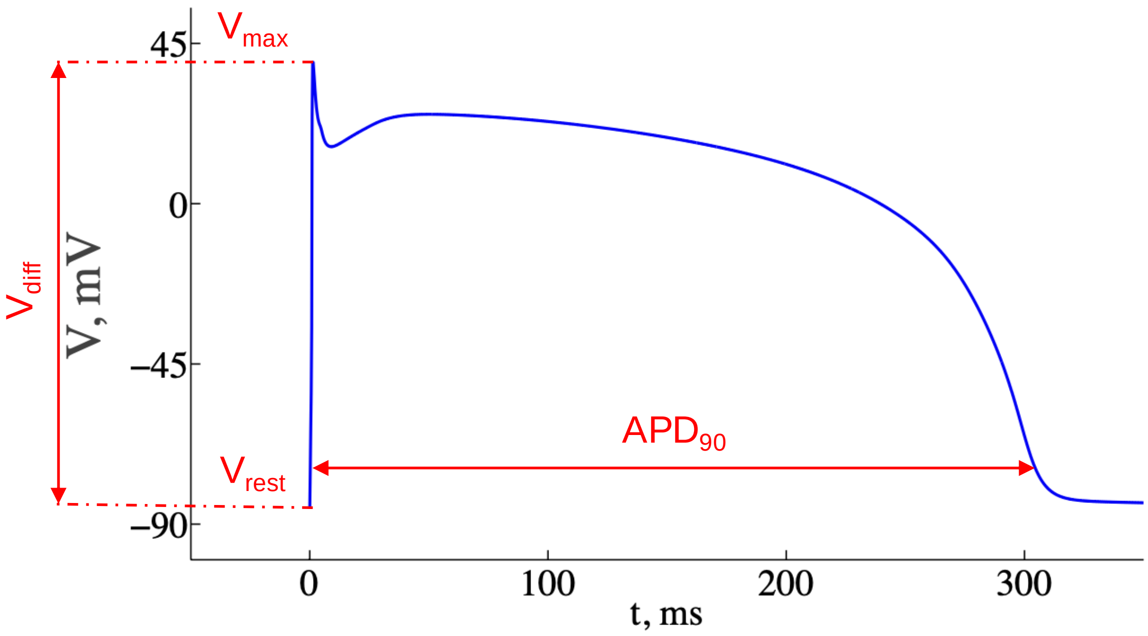


applications:

- hypertension
- Angina Pectoris
- supraventricular arrhythmias
- anaeurisms
- heart failure

Objectives

Effects of **diltiazem** on atrial cardiomyocyte:
blockage of **L-type calcium** channels



1. Waveforms changes
2. V_{rest} and V_{max}
3. V_{diff}
4. APD_{90}

Materials

Maleckar model (2009):

model of the human atrial cardiomyocyte AP
(30 state variables)

based on the Nygren et al. Model (2001)

changes characteristics of I_{K1}, I_t, I_{Kur}

accurate representation of AP and repolarization phase

Matlab simulation

Methods

Settings parameters

BCL = 800 ms → time between two consecutive stimuli

Dur_stim = 1 ms → duration of the stimulation

NumStim = 30 → number of stimulations

TSim = 24000 ms → simulation time → 800 ms * 30

Amp_stim = -42 mV → amplitude of the stimulation → 1.5*threshold = 1.5 * (-28mV)

% conductance of L-type Ca channels

Const = [1 0.95 0.9 0.85 0.8 0.75 0.7 0.65 0.6 0.55 0.5 0.45 0.4 0.35 0.3 0.25 0.2 0.15 0.1 0.05 0.0];

g_{Ca_L} = 6.75 nS * Const

Methods

Waveforms

1. Plots of 30 APs and then the last one, by setting storeLast
- Plots of the ionic currents

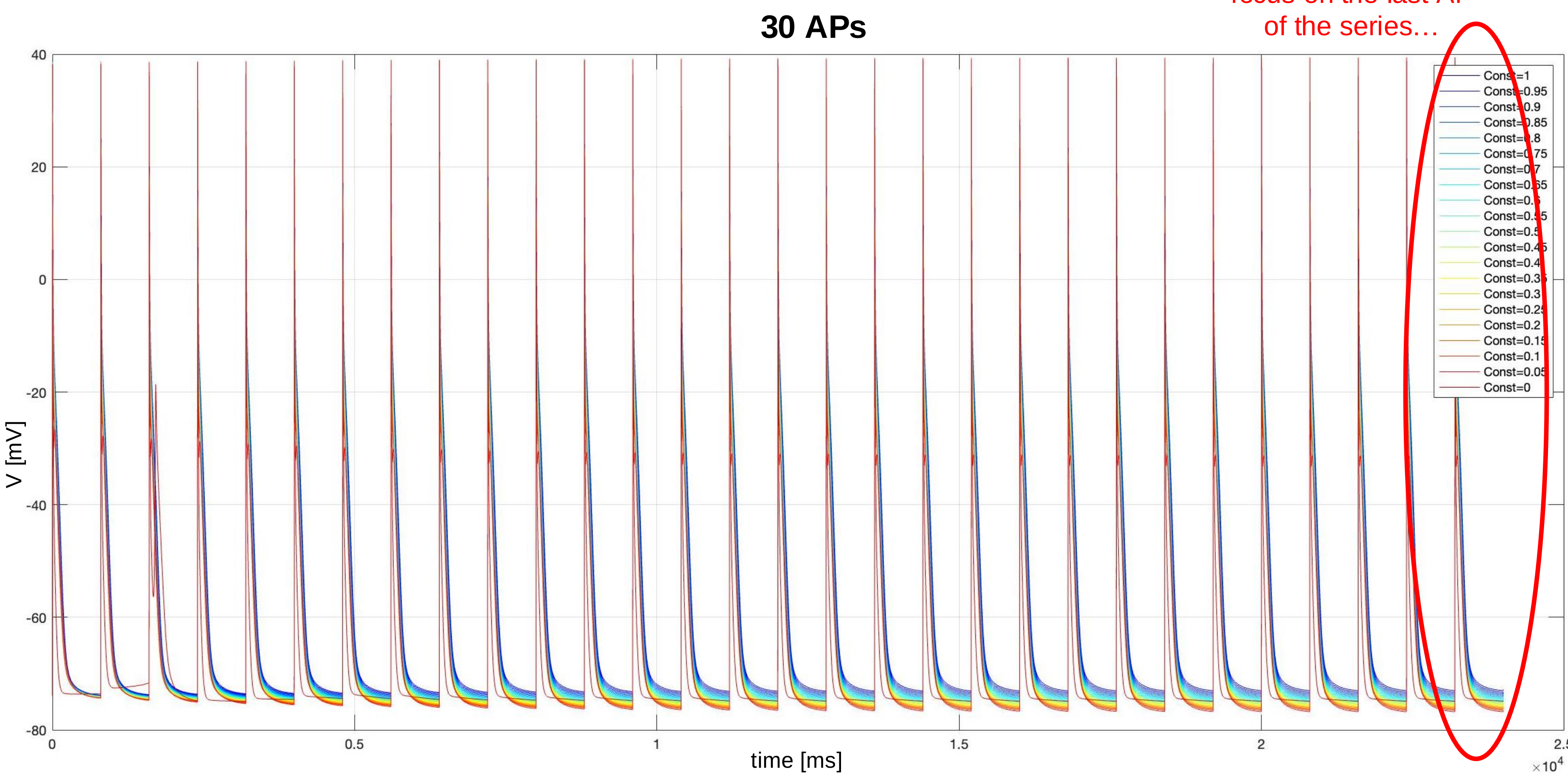
Measurement of the following parameters for the last AP

2. V_{rest} = min AP and V_{max} = max AP
3. $V_{diff} = V_{max} - V_{rest}$
- $V_{90} = V_{max} - 0.9 * V_{diff}$ → corresponds to 90 % of repolarization
- t_0 → corresponds to the time for which $V = V_{max}$
- t_{90} → corresponds to the time for which $V = V_{90}$

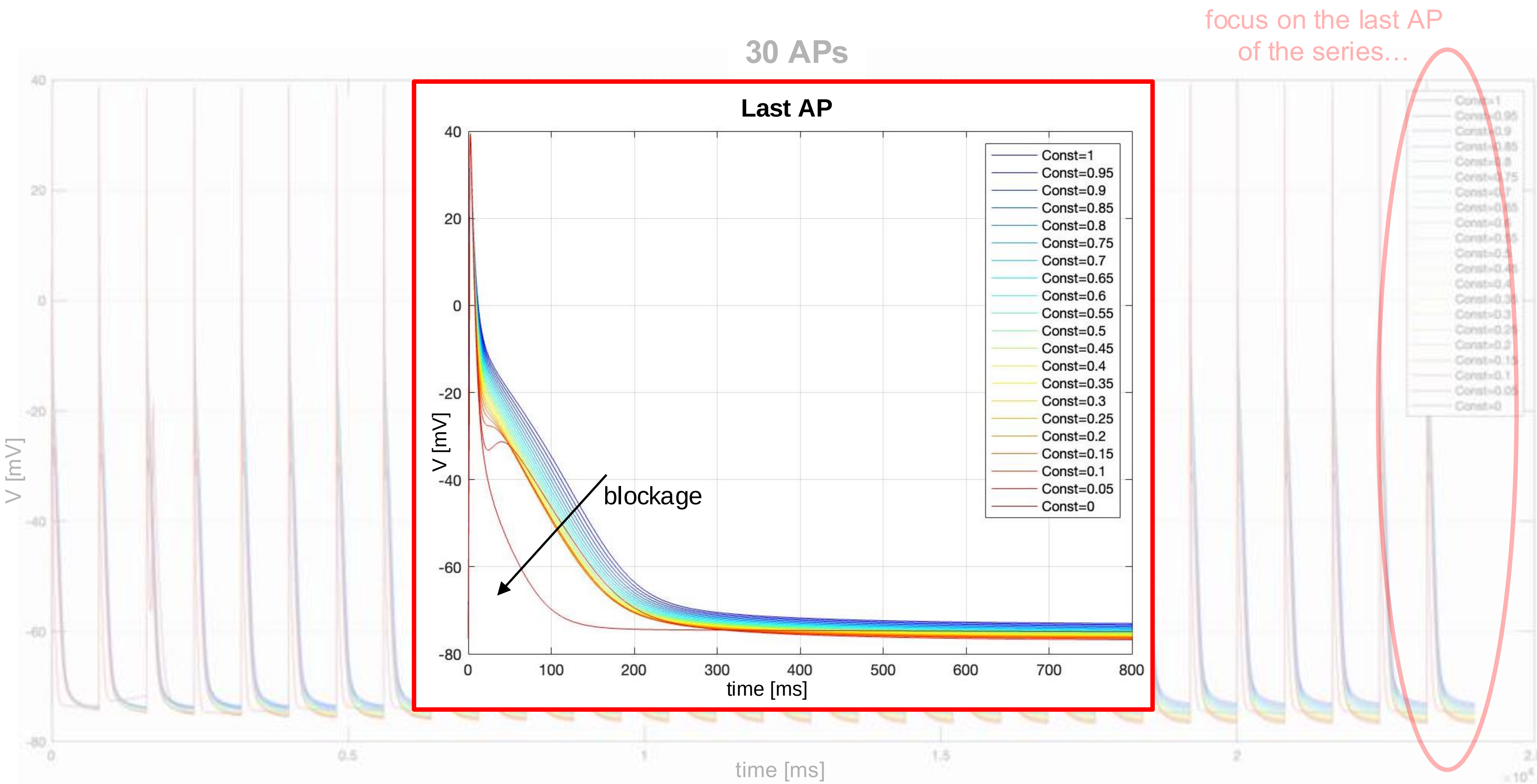
4. $APD_{90} = t_{90} - t_0$ → corresponds to AP duration at 90% of repolarization

Results and discussion: action potential

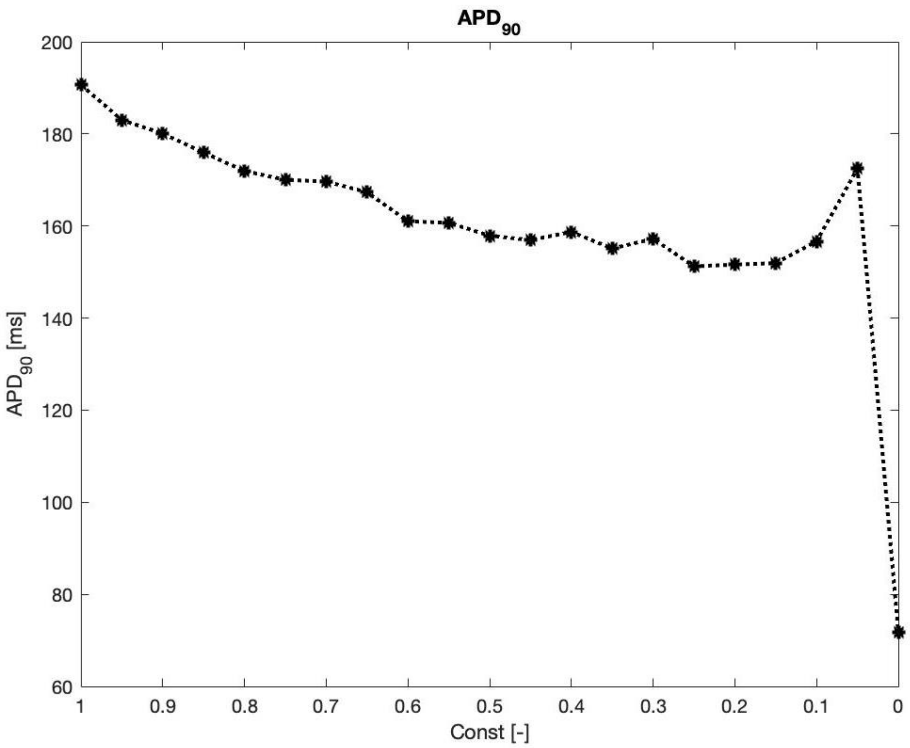
focus on the last AP of the series…

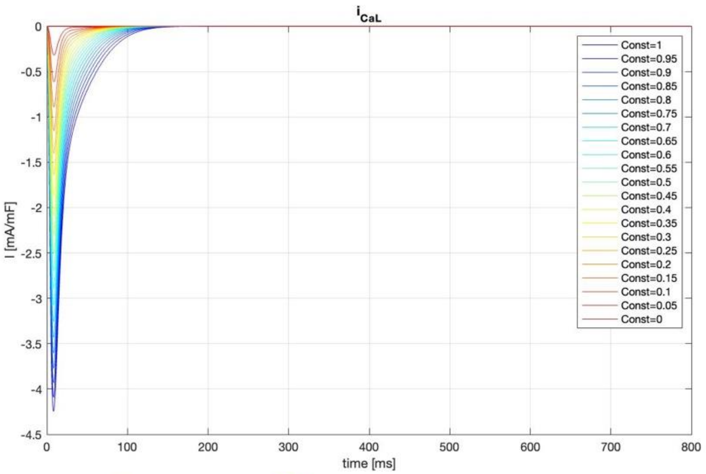


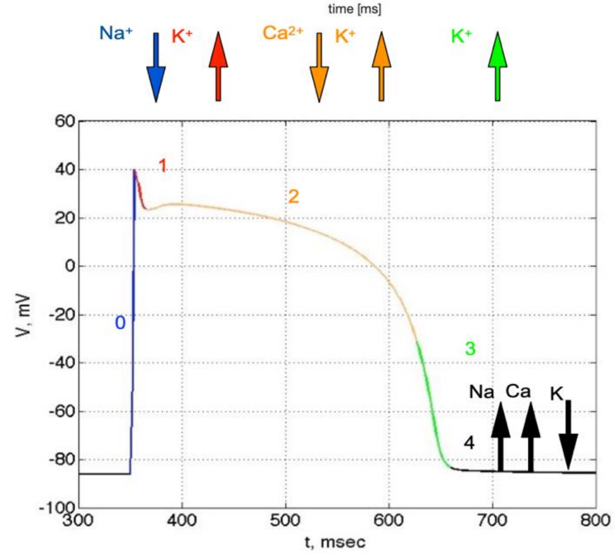
Results and discussion: action potential



Results and discussion: APD_{90}

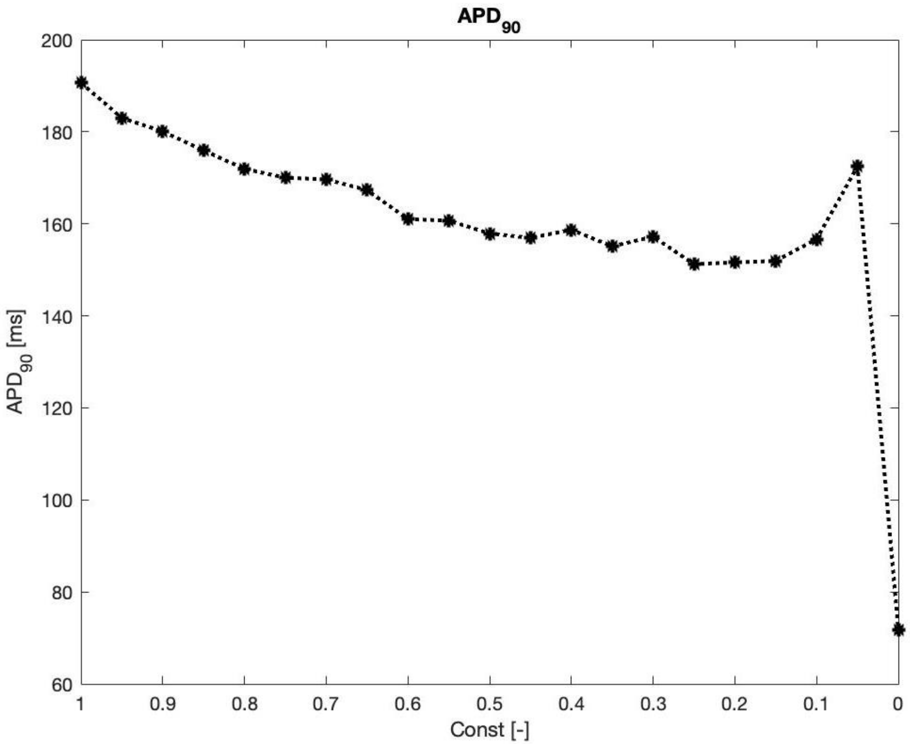


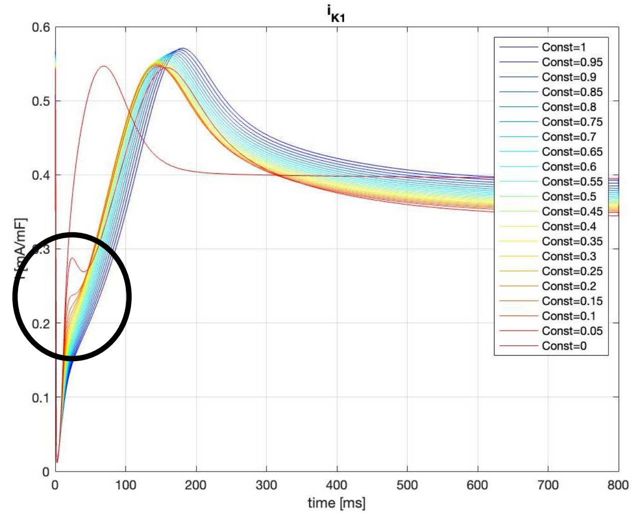


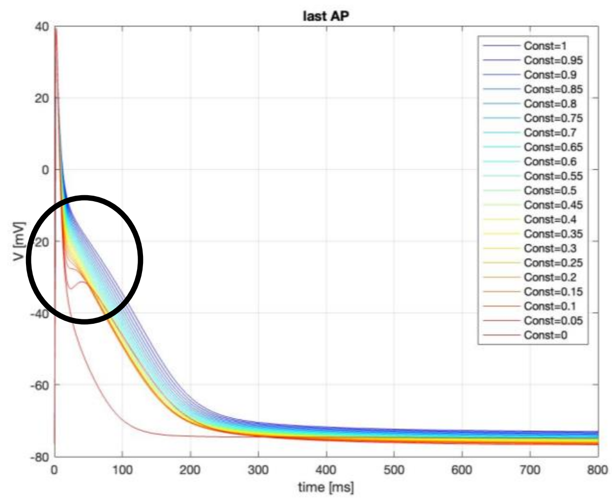


- In general, **decreases**: **Ca** responsible of plateau phase → shorter duration of depolarization

Results and discussion: APD_{90}

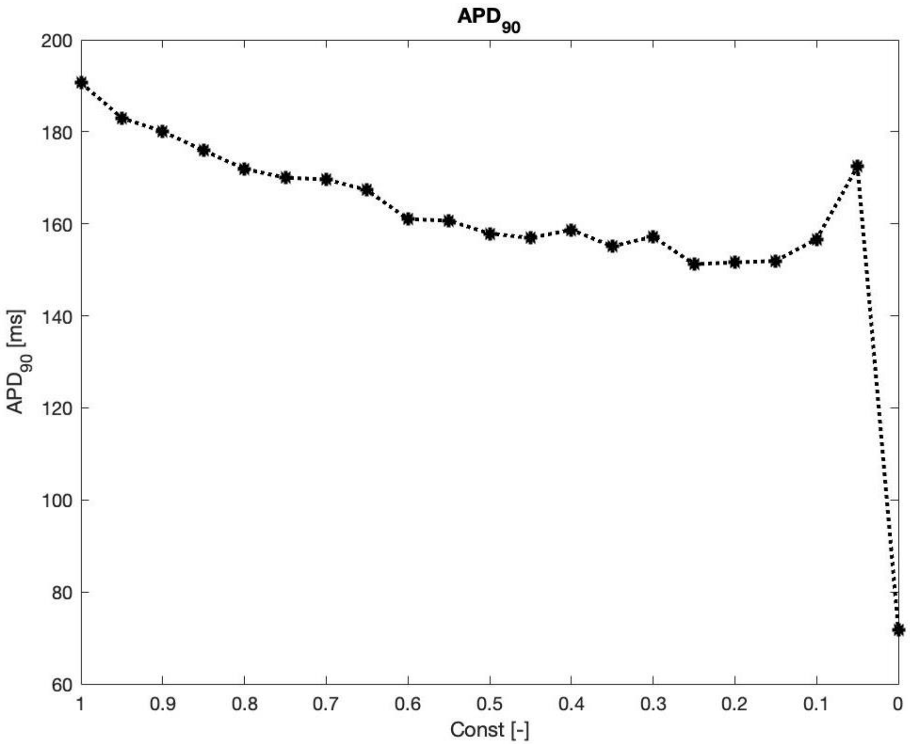


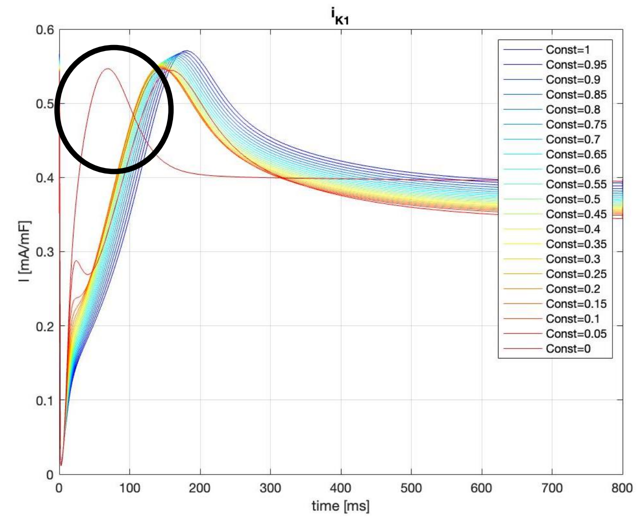


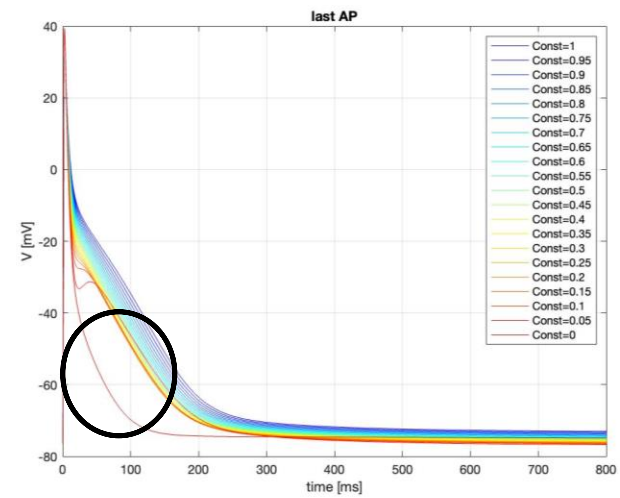


- For **low values** of Const, APD_{90} **increases** slightly → an early peak appears in $\mathbf{I_{K1}}$ → distortion in the AP

Results and discussion: APD_{90}

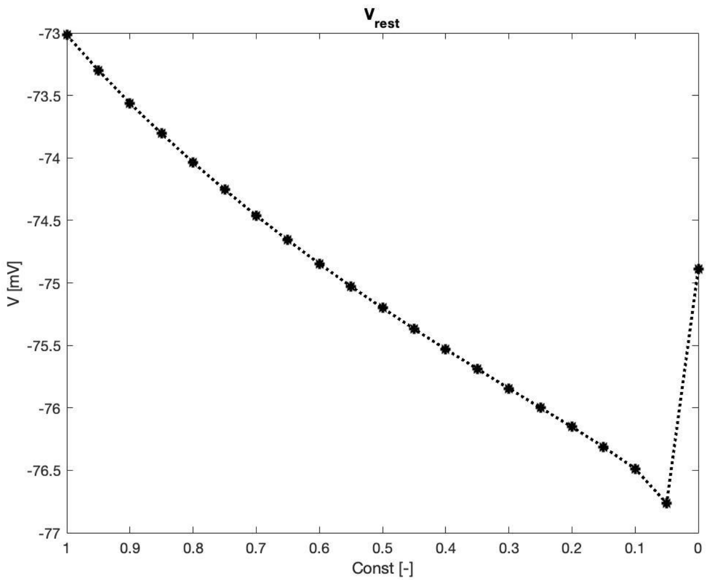


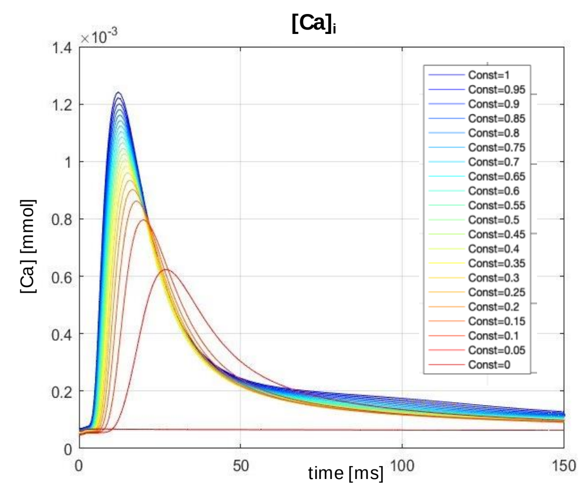


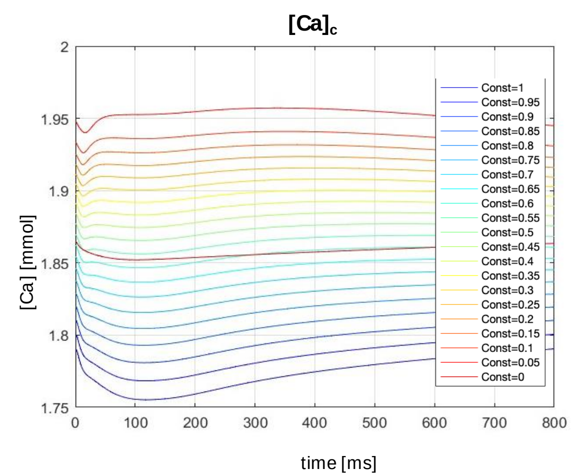


- For **low values** of Const, APD_{90} **increases** slightly → an early peak appears in $\mathbf{I_{K1}}$ → distortion in the AP
- For **Const = 0**, APD_{90} **decreases** → **no Ca** and $\mathbf{I_{K1}}$ peak appears **earlier** → more rapid repolarization

Results and discussion: V_{rest}







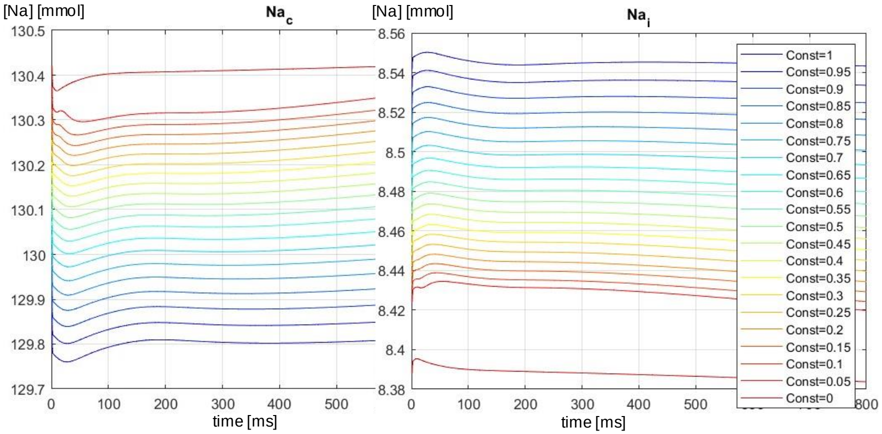
- In general, **V_{rest} decreases** → GHK equation

$$\boxed{V_{rest} = \frac{R*T}{F} * \ln \frac{P_K*[K^+]_o + P_{Na}*[Na^+]_o + P_{Cl}*[Cl^-]_i + P_{Ca}*[Ca^{2+}]_o}{P_K*[K^+]_i + P_{Na}*[Na^+]_i + P_{Cl}*[Cl^-]_o + P_{Ca}*[Ca^{2+}]_i}}$$

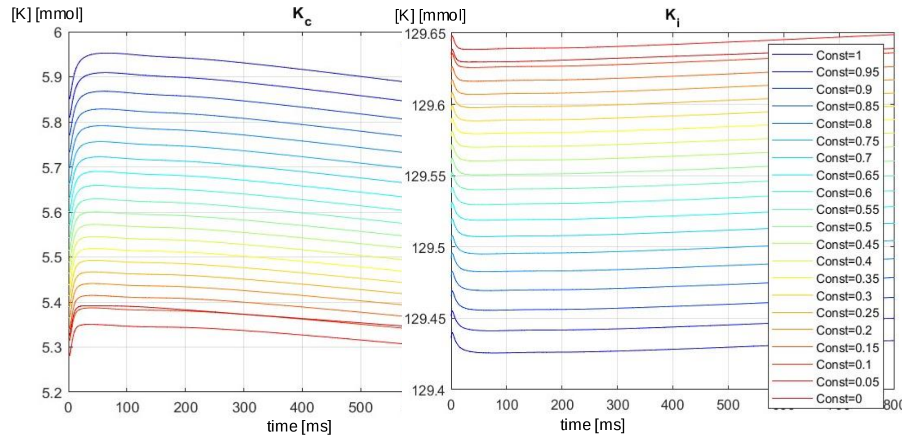
- **$[Ca]_i$ and $[Ca]_c$** vary, but ~ **no effect** on Vrest because too low permeability
- Ca_L channel blockage → **effects** on other **currents** → **[K] and [Na]** change

→ V_{rest} changes

Results and discussion: V_{rest}



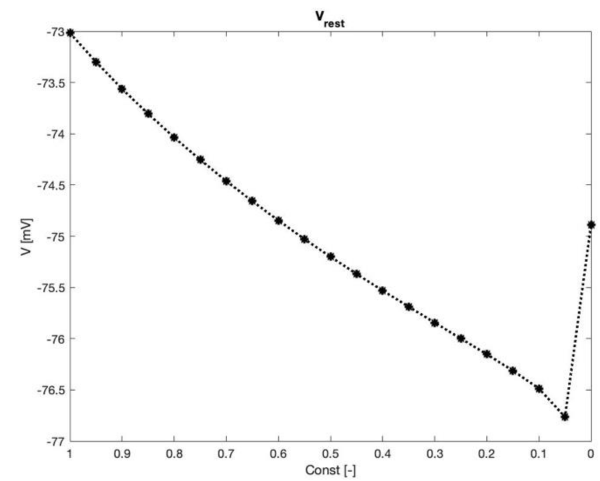
$[Na]_o \uparrow$ $[Na]_i \downarrow$ → ratio becomes higher
→ V_{rest} should increase



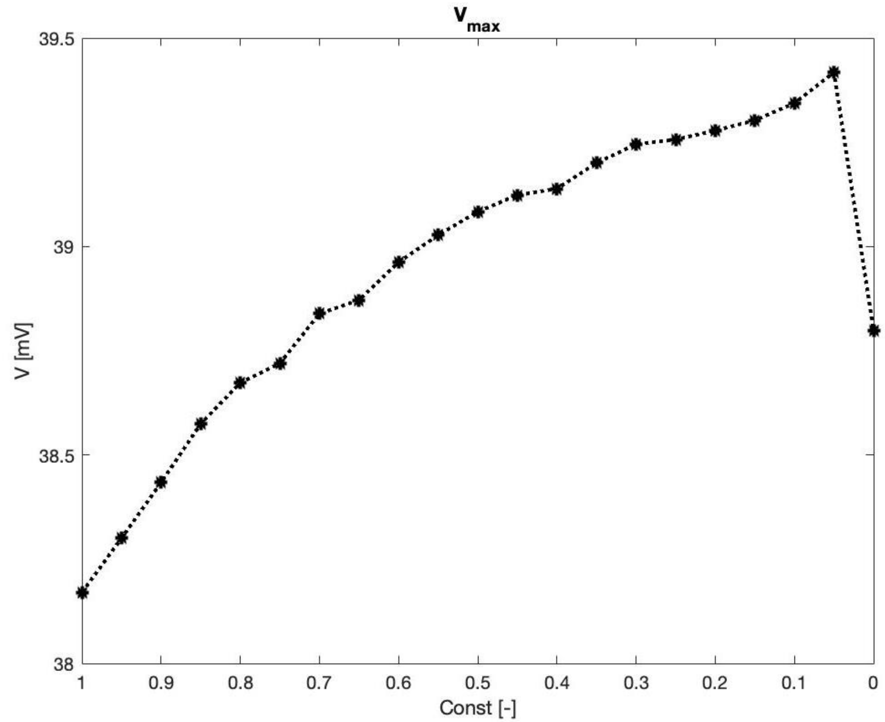
$[K]_o \downarrow$ $[K]_i \uparrow$ → ratio becomes lower
→ V_{rest} should decrease

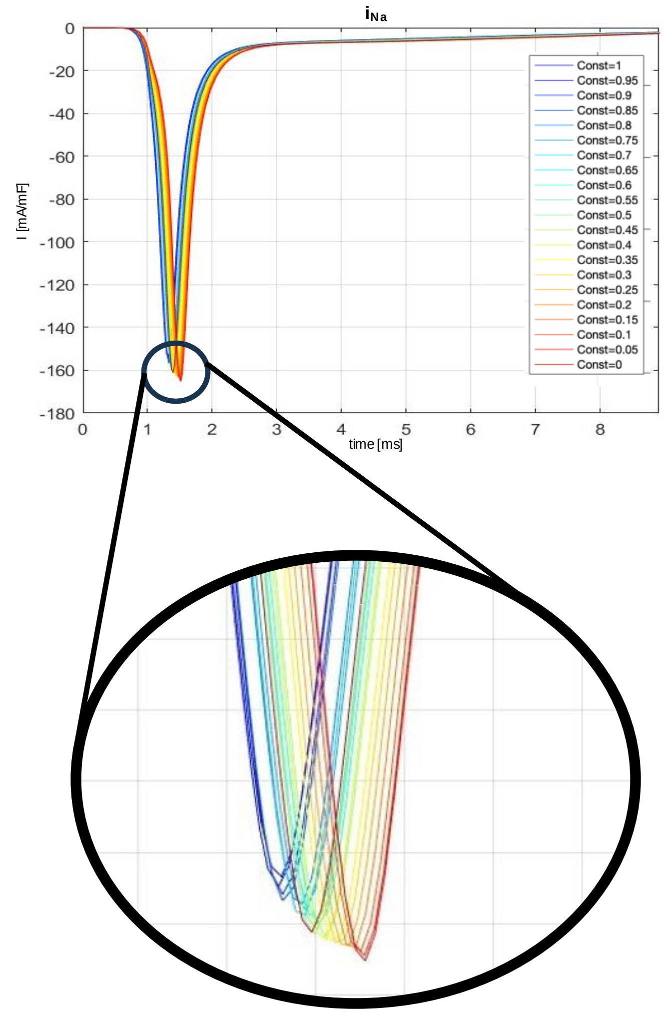
$$\boxed{V_{rest} = \frac{R*T}{F} * \ln \frac{P_K * [K^+]_o + P_{Na} * [Na^+]_o + P_{Cl} * [Cl^-]_i + P_{Ca} * [Ca^{2+}]_o}{P_K * [K^+]_i + P_{Na} * [Na^+]_i + P_{Cl} * [Cl^-]_o + P_{Ca} * [Ca^{2+}]_i}}$$

- In general, **V_{rest} decreases** because [K] has a bigger influence
- **For Const = 0**: $[Na]i \downarrow$ a lot so **V_{rest} increases** a little



Results and discussion: V_{max}





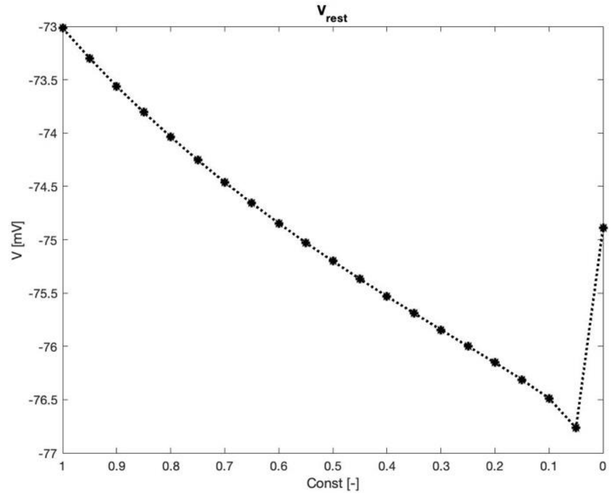
- In general :

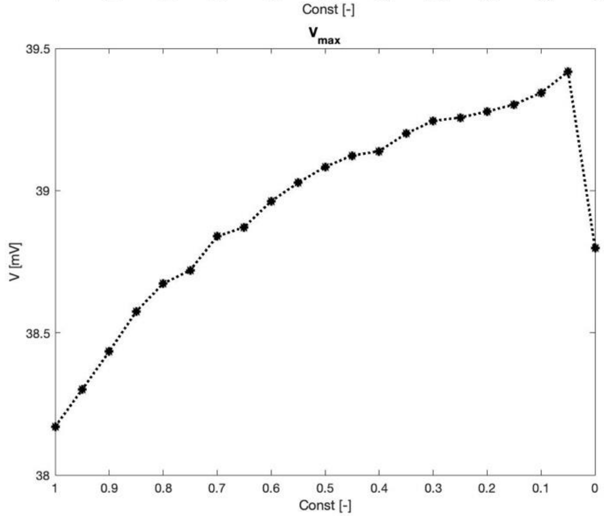
$i_{Na}\uparrow$ → more depolarized → **greater** V_{max} peak

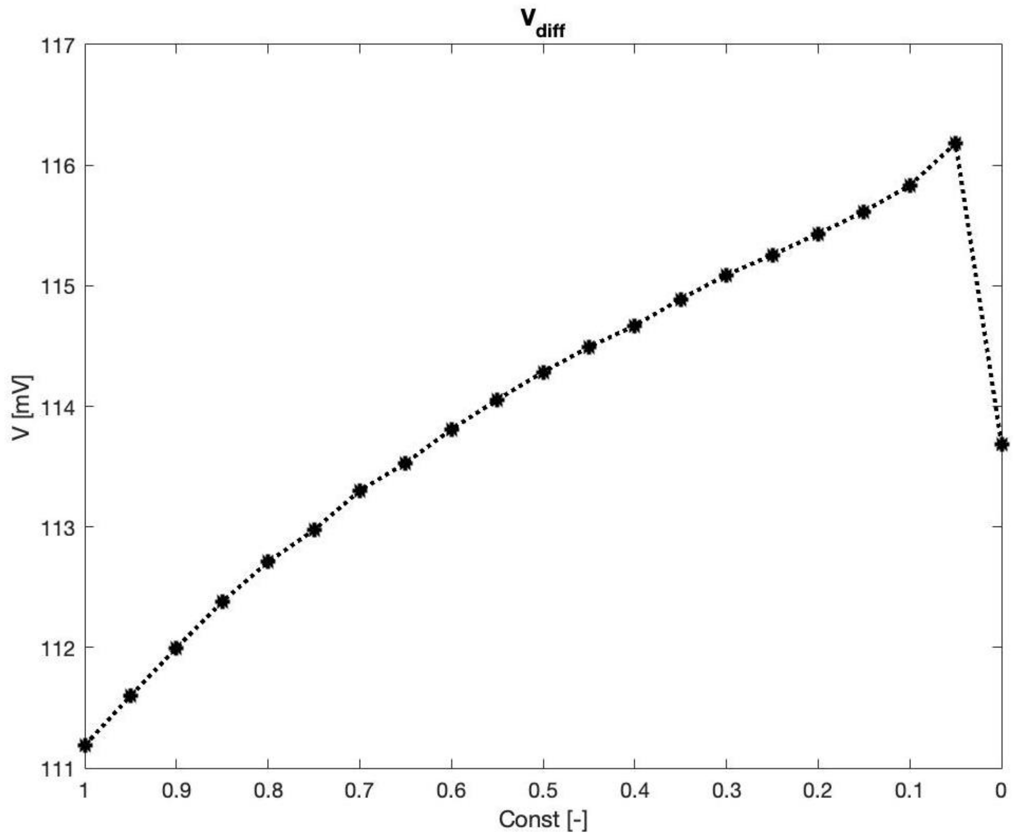
- For **Const = 0**

$i_{Na}\downarrow$ → less depolarized → **decrease** in V_{max}

Results and discussion: V_{diff}

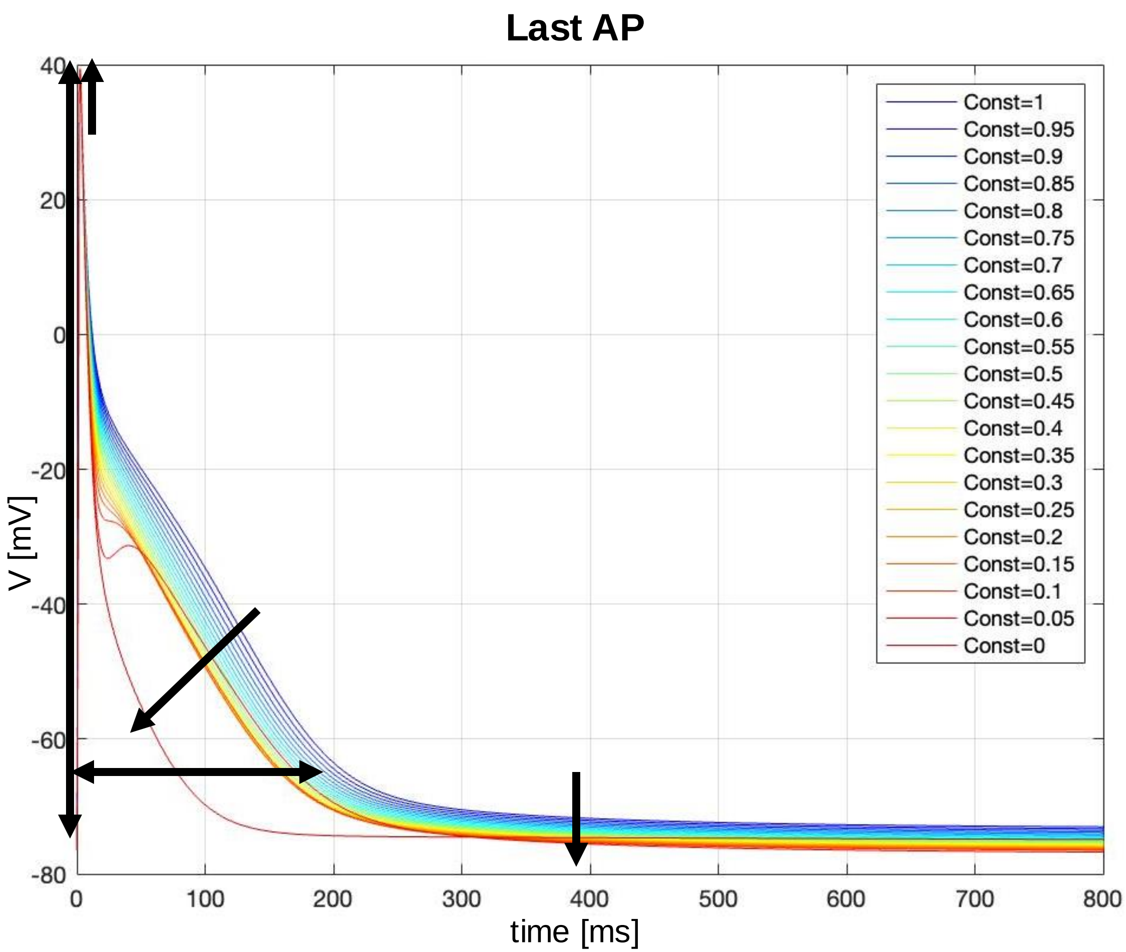






- V_{diff} increases until Const = 0.05
- For Const = 0, V_{diff} falls down

Conclusions



In general:

- V_{rest} decreases,
  V_{max} increases
  └→ V_{diff} increases
- Repolarization more and more rapid → no plateau
- APD_{90} decreases

For low Const values:

- Abnormal behaviour

Conclusions

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- Better representation of the currents
- Good representation of human atrial cardiomyocyte bioelectric activity

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- Very simplified model (Hodgkin-Huxley formalism and Ca channels)
- Small dataset
- Heterogeneities in AP

Bibliographic references

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Thanks for your attention!

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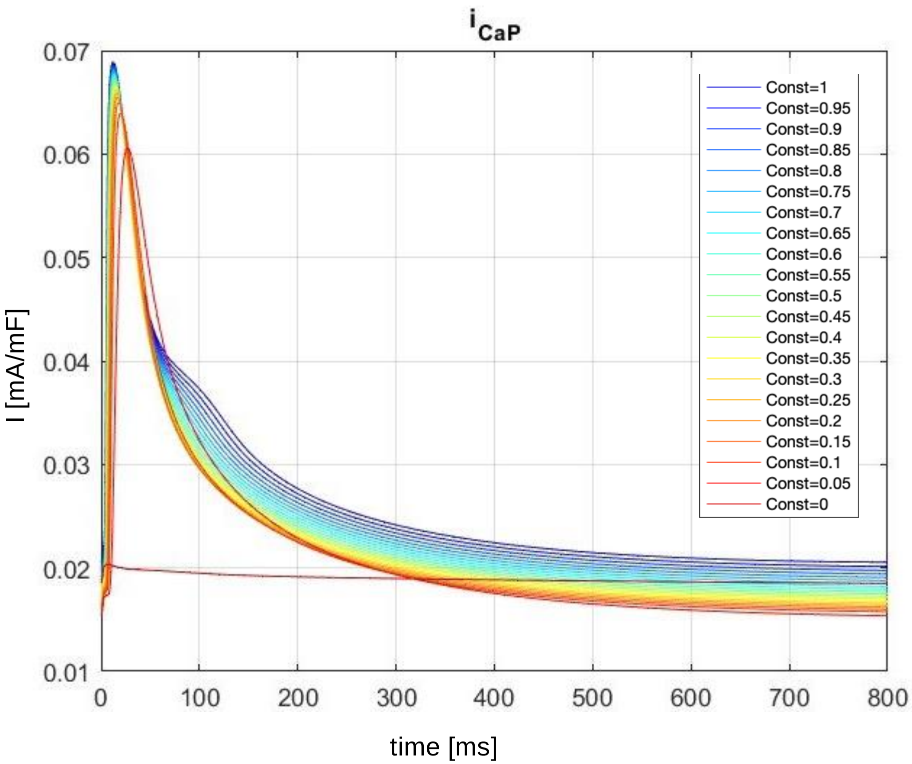
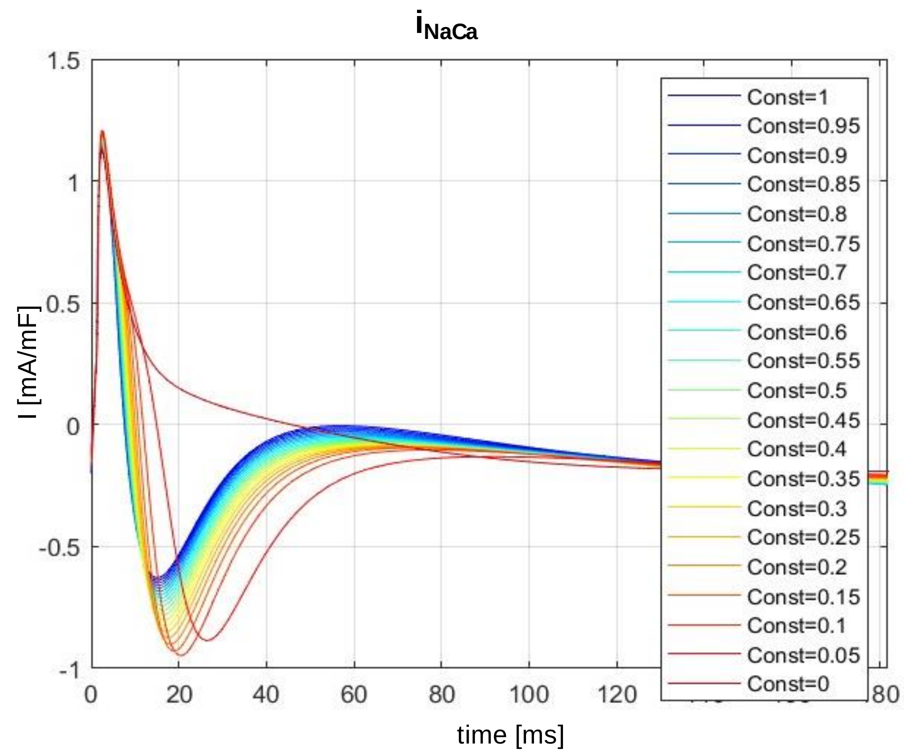
Additional slides: Ca currents

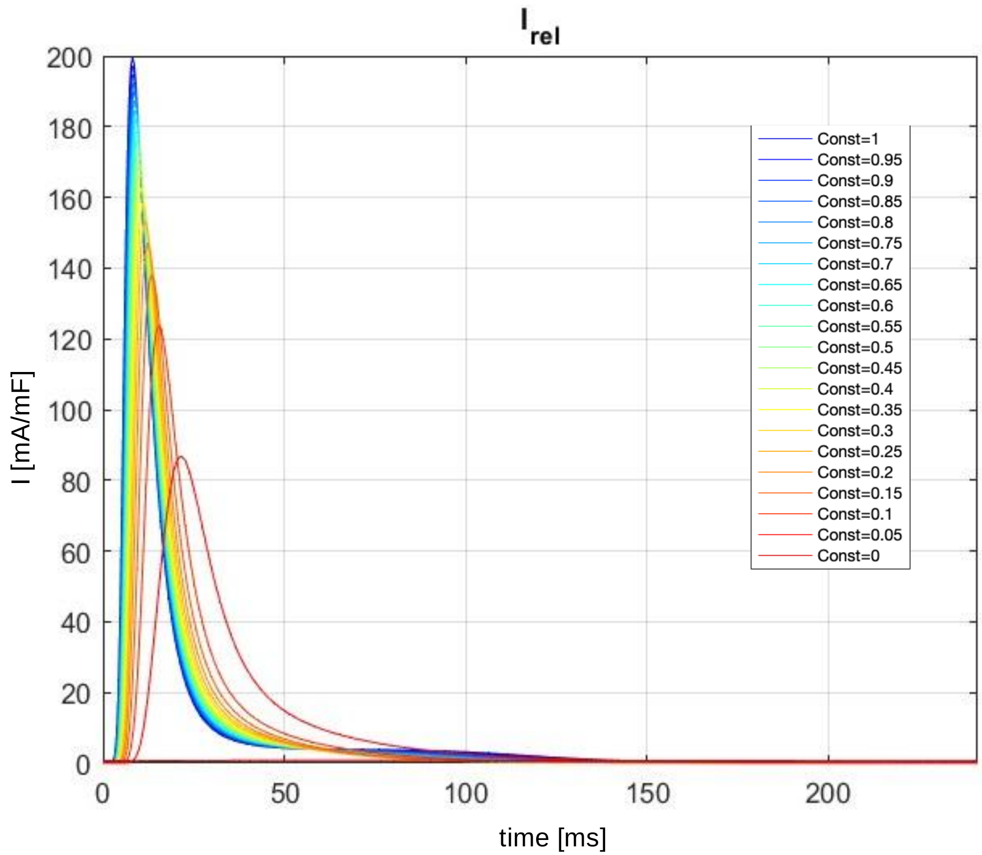


(sarcolemmal Ca pump)



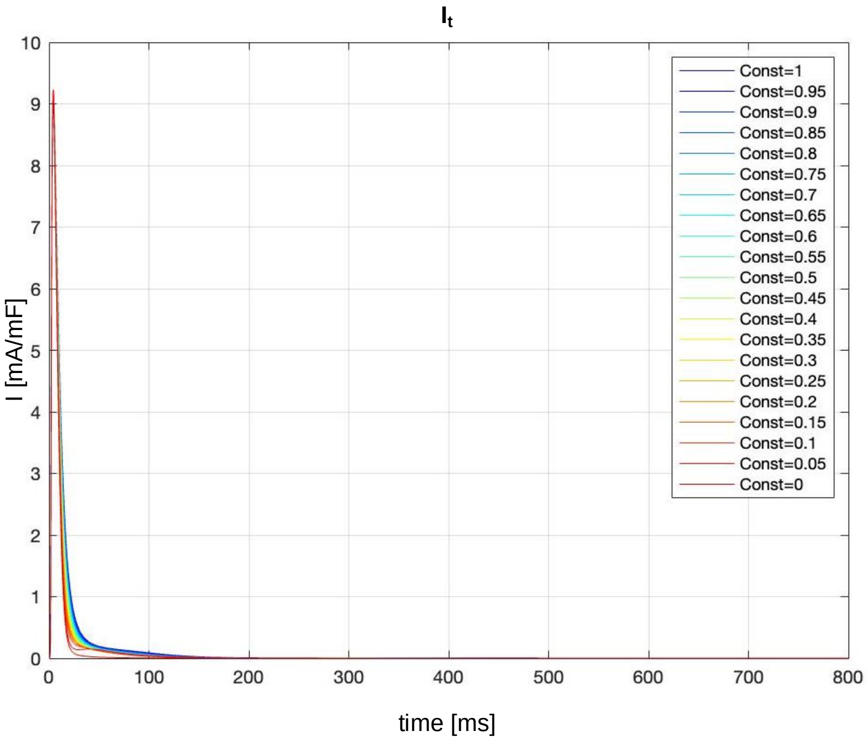
(Na-Ca exchanger)

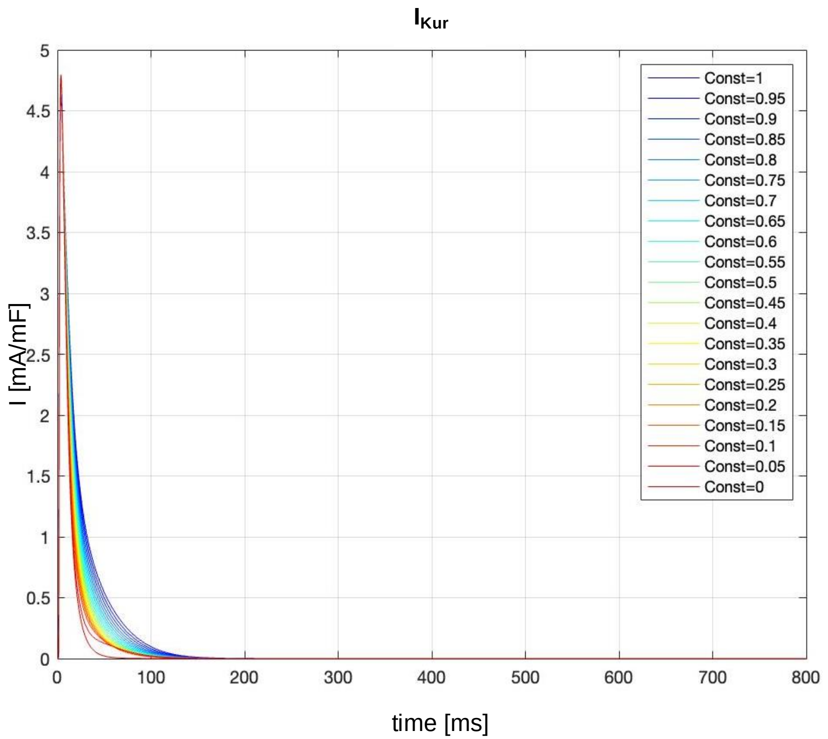
Additional slides: Ca currents



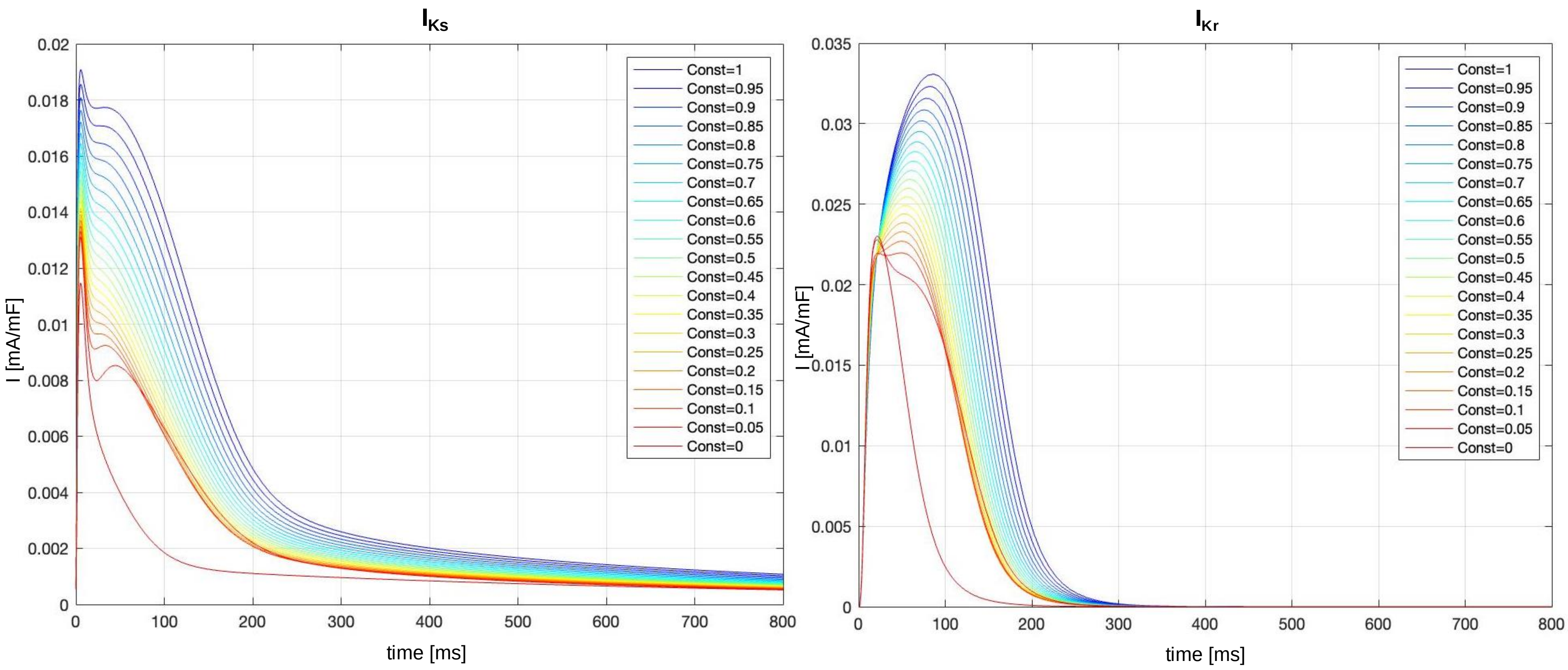
(sarcoplasmic reticulum RyR channel)

Additional slides: other currents

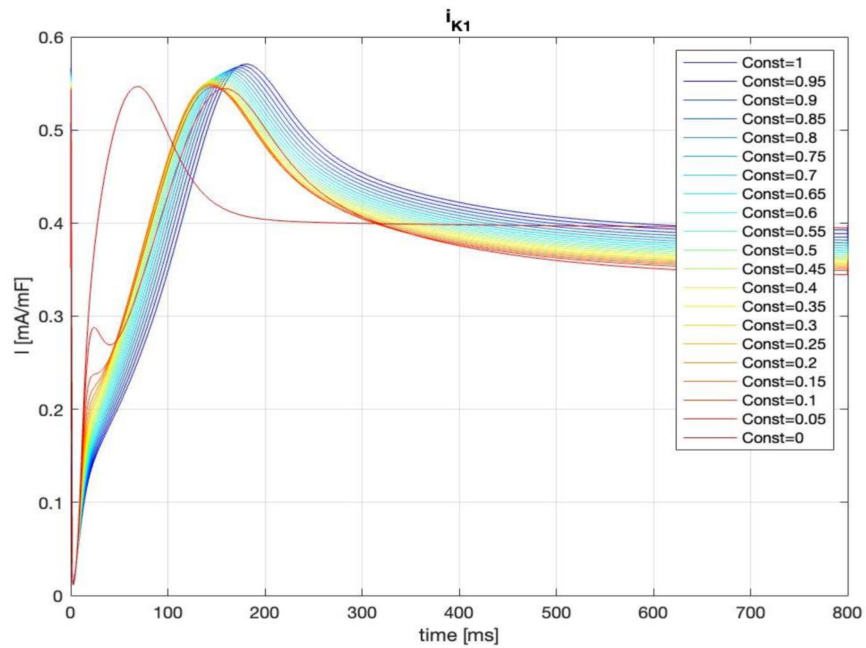


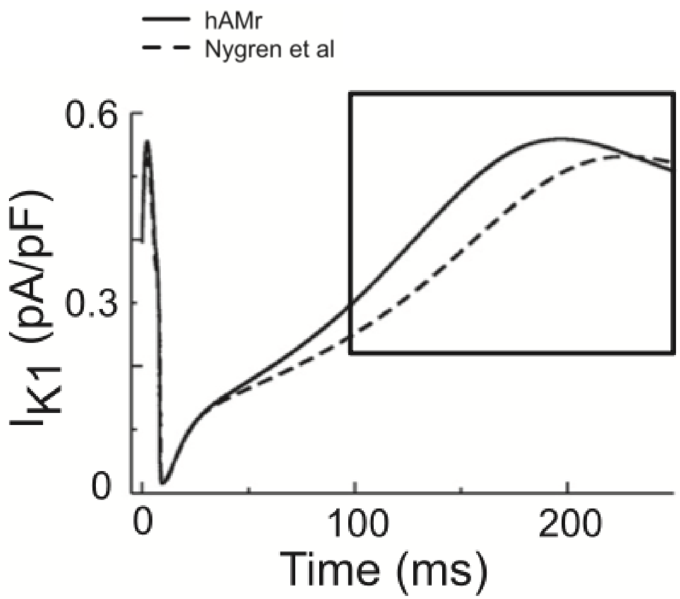


Additional slides: other currents

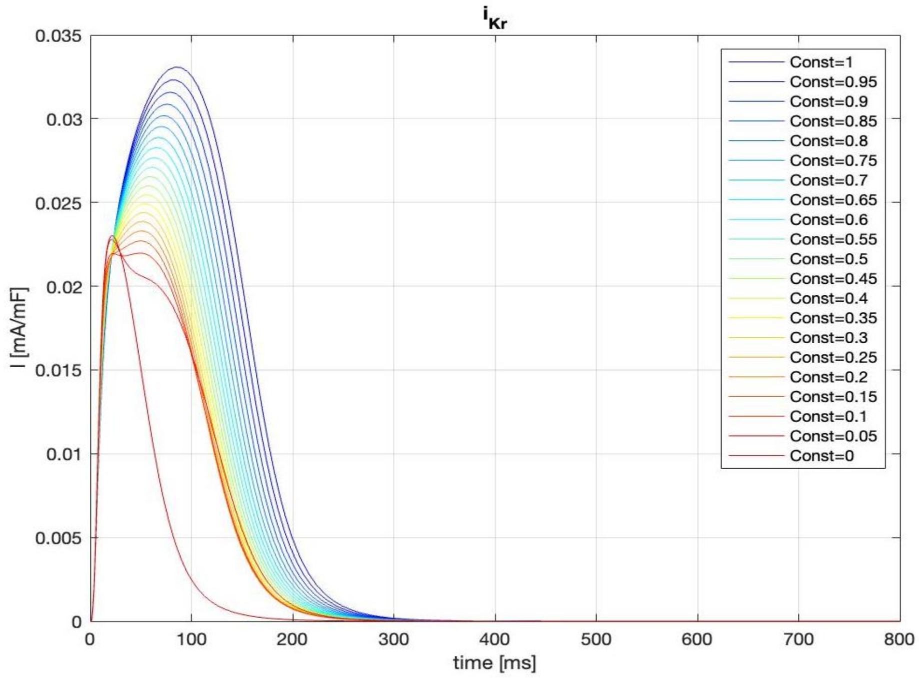


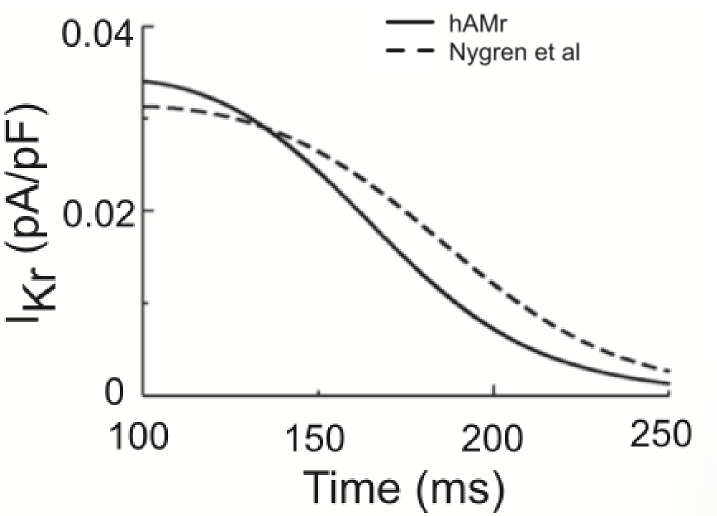
Additional slides: our currents VS model (I_{K1})



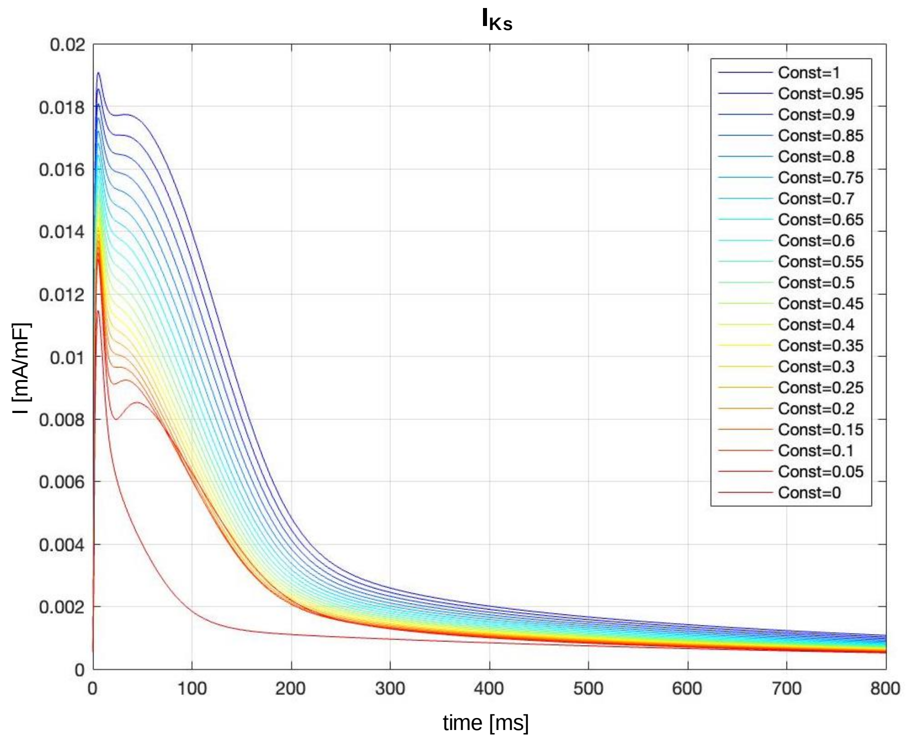


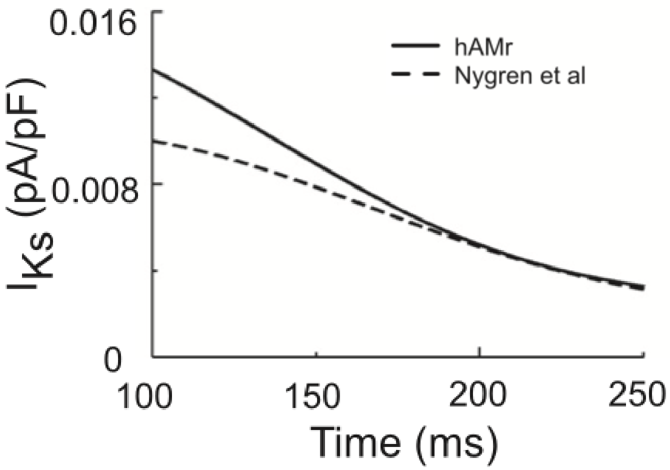
Additional slides: our currents VS model (I_{kr})



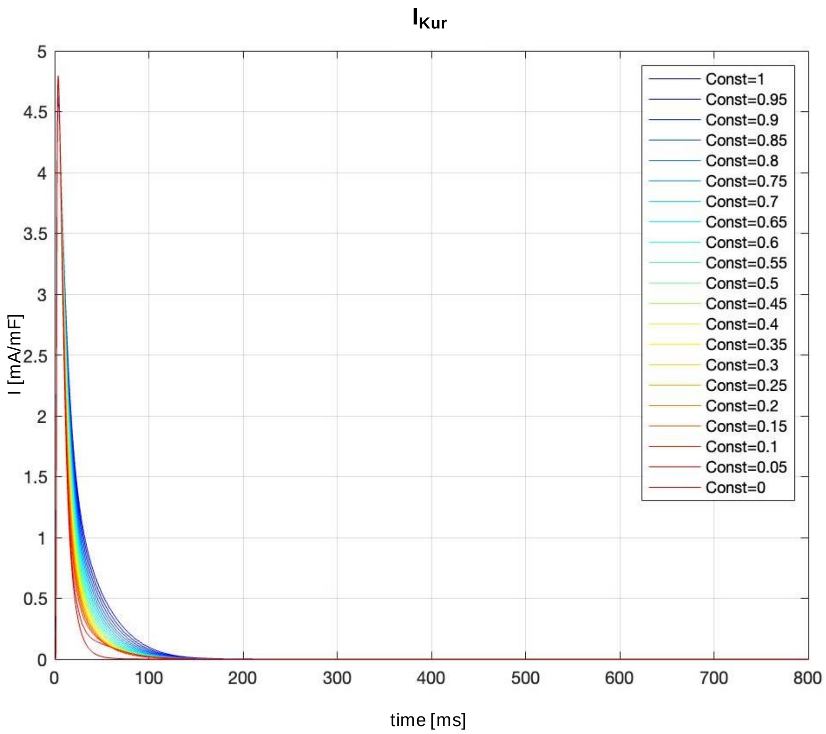


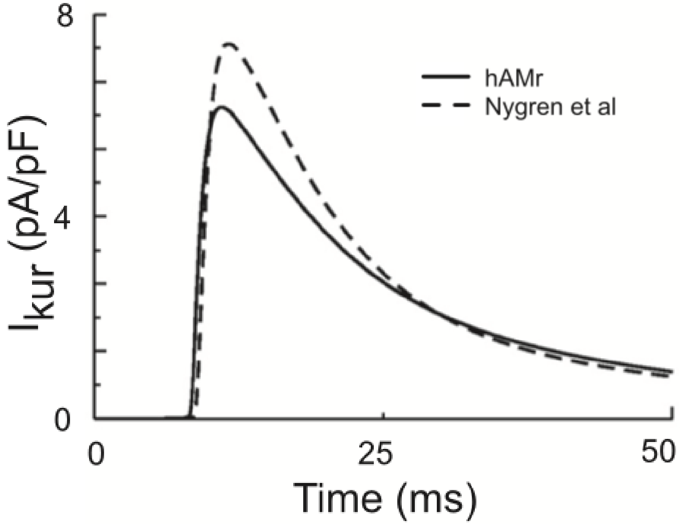
Additional slides: our currents VS model (I_{Ks})





Additional slides: our currents VS model (I_{Kur})





Additional slides: our currents VS model (I_t)