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**Article:**

Bernjak, A., Iqbal, A., Heller, S. et al. (2021) Hypoglycaemia combined with mild hypokalaemia reduces the heart rate and causes abnormal pacemaker activity in a computational model of a human sinoatrial cell. *Journal of the Royal Society Interface*, 18 (184). 20210612. ISSN: 1742-5689

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## Supplementary Material

### Hypoglycaemia combined with mild hypokalaemia reduces the heart rate and causes abnormal pacemaker activity in a computational model of a human sinoatrial cell

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Journal of the Royal Society Interface

#### Methodology

##### Model of the human sinoatrial node AP

The Fabbri model (1) includes ion channels, pump/exchanger mechanisms and intra- and extracellular ion concentrations as well as complex intracellular calcium handling. Calcium currents have a major role in the pacemaker activity of the SA node and this was confirmed in this model. Fabbri et al showed that the permeability of the L-type  $\text{Ca}^{2+}$  channel is positively and substantially correlated with the rate of rise in membrane potential in the depolarisation phase, as well as with action potential duration (APD). The activation kinetics of this channel also has a strong impact on the cycle length (CL) of the pacemaker activity and intracellular calcium transients.

In addition to baseline electrophysiology, the modulation of the pacemaker rate in response to autonomic stimulation was adapted from the Severi rabbit model. In the rabbit model, acetylcholine (ACh)- and isoprenaline (Iso)-induced variations in pacemaker rate were introduced to mimic the activation of the sympathetic (increased rate) and parasympathetic (decreased rate) nervous system, respectively. Adjustments were made to fit experimental data. Briefly, the action of ACh was simulated by blocking the  $I_{\text{Ca,L}}$  current and sarcoplasmic reticulum  $\text{Ca}^{2+}$  uptake, shifting the  $I_f$  activation curve and activating  $I_{\text{K,ACh}}$ . The action of Iso was simulated by shifting the  $I_f$  activation curve and by modulating  $I_{\text{Ca,L}}$ ,  $I_{\text{Ks}}$ ,  $I_{\text{NaK}}$ , and the sarcoplasmic reticulum  $\text{Ca}^{2+}$  uptake rate. In the human model, Fabbri et al adopted these settings, which produced a 21% decrease in heart rate (from 74bpm to 59bpm) in response to ACh and a 28% increase in rate (from 74bpm to 95bpm) in response to Iso.

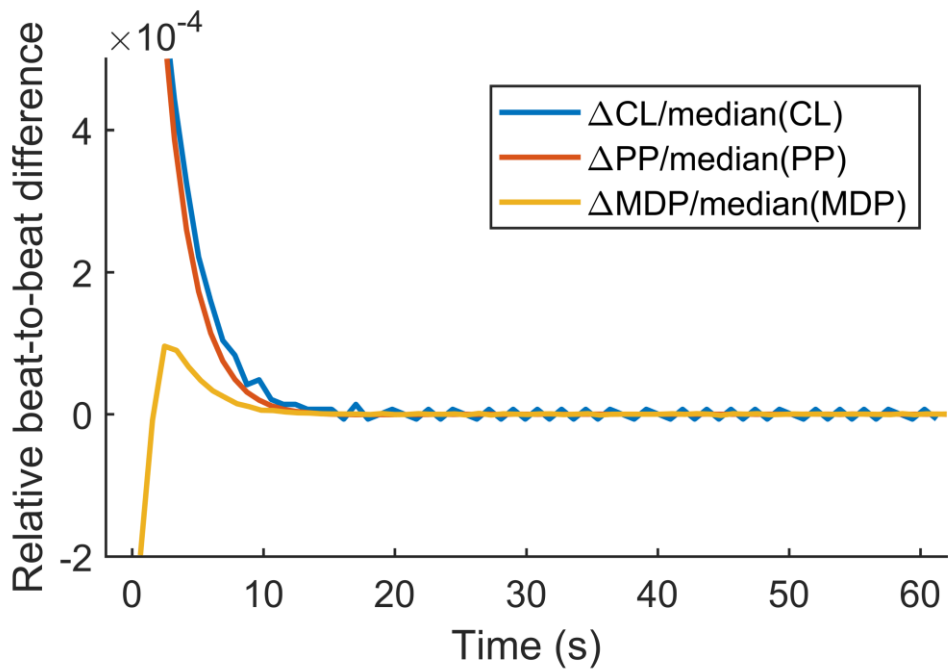
##### Stability of the main features of the AP waveform

The steady-state condition of the Fabbri model was determined at 50s by Fabbri et al. We confirmed the stability of the main features of the AP waveform (CL, PP and MDP) in our model by plotting the beat-to-beat changes in each parameter relative to their median value over the duration of simulation (Supplementary Figure 1). To avoid large beat-to-beat variability due to discretisation error we increased the sampling resolution of the action potential waveforms using cubic spline interpolation.

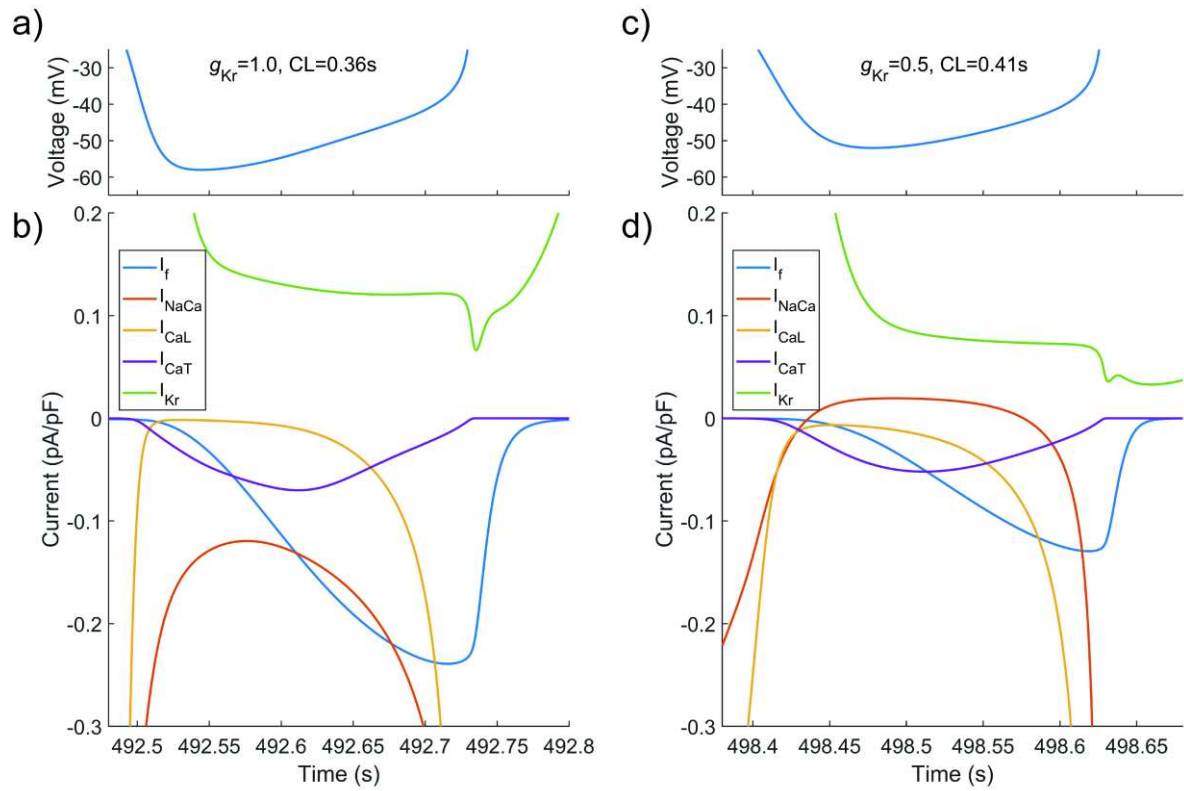
#### Reference:

1. Fabbri A, Fantini M, Wilders R, Severi S. Computational analysis of the human sinus node action potential: model development and effects of mutations. *J Physiol.* 2017;595(7):2365–96. <http://doi.wiley.com/10.1113/JP273259>

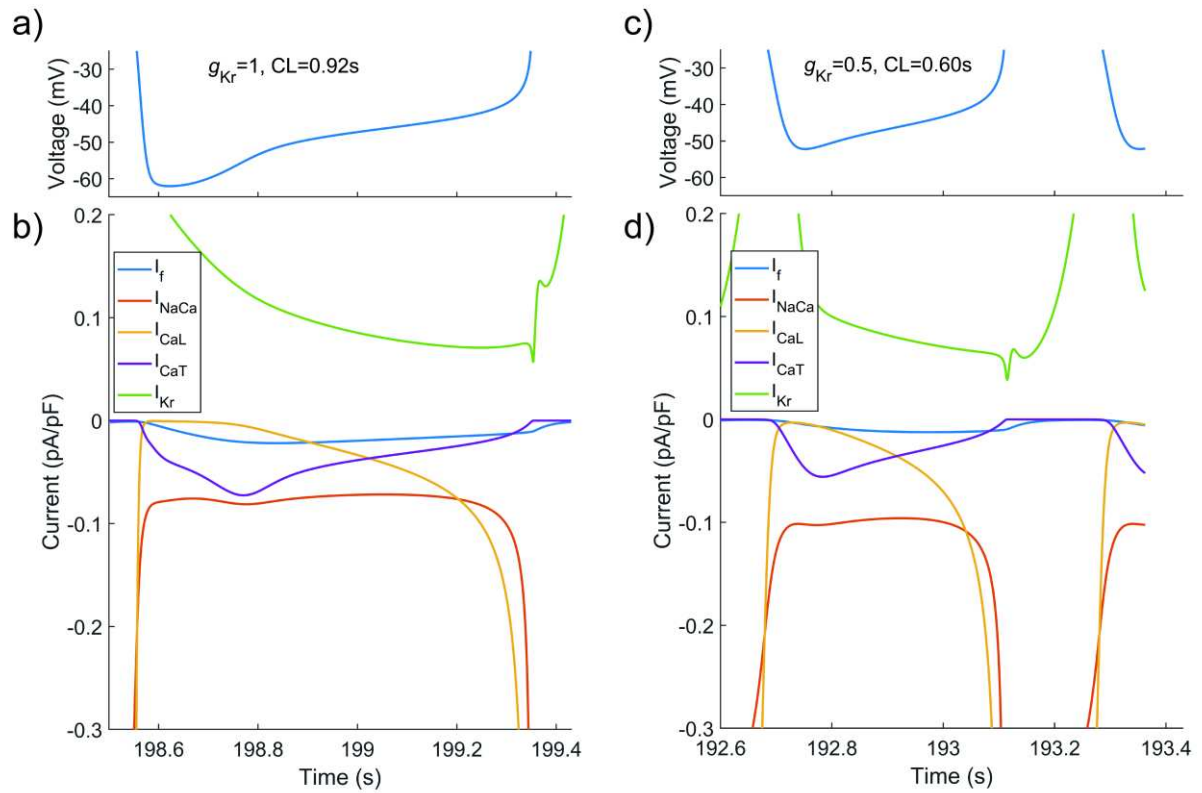
## Supplementary Figures:



Supplementary Figure S1: Stability of AP features: CL, PP and MDP. Beat-to-beat differences in parameter values, normalised to their median value over the 600s simulation are plotted. AP waveforms were upsampled using cubic spline interpolation. The beat-to-beat variability for all parameters is stable after about 20s.



Supplementary Figure S2: The major membrane currents underlying diastolic depolarisation in the computational model of the rabbit SA node. The AP waveforms (a,c) and normalised currents (b,d) are presented at baseline ( $g_{K_r}=1$ ) (a,b) and with reduced conductance ( $g_{K_r}=0.5$ ) (c,d).



Supplementary Figure S3: The major membrane currents underlying diastolic depolarisation in the computational model of the human SA node. The AP waveforms (a,c) and normalised currents (b,d) are presented at baseline ( $g_{K_r}=1$ ) (a,b) and with reduced conductance ( $g_{K_r}=0.5$ ) (c,d).