Noninvasive evaluation of cardiac repolarization in mice exposed to single-wall carbon nanotubes and ceria nanoparticles via intratracheal instillation


Joint School of Nanoscience and Nanoengineering, University of North Carolina at Greensboro and North Carolina Agricultural and Technical State University, 2907 E Gate City Boulevard, Greensboro, NC 27401

Supplemental Material: Mathematical Details

In this section, we describe the mathematical procedure for computing the RoR from a pair of QT and RR interval measurements acquired form an ECG signal. The two-variable CSC model for propagation of electrical excitation pulses is given [1] by Eqs. (1).

\[
\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial t^2} - i(u,v)
\]

\[
\frac{\partial v}{\partial t} = \varepsilon(\zeta u + v_r - v)
\]

\[
i(u,v) = \begin{cases} 
\lambda u & (u < v) \\
u - 1 & (u \geq v)
\end{cases}
\]

Here, $u$ corresponds to dimensionless cellular transmembrane potential and $v$ is the dimensionless recovery current. The singular limit ($\varepsilon \ll 1$) of Eqs. (1) corresponds to rectangular pulses for which the variable $u$ abruptly switches between its maximum and minimum values, as depicted in Fig. 1. Within this limit, one may analytically obtain expressions for the
dimensionless RR and QT intervals in terms of system parameters through a simple integration of Eqs.(1), obtaining:

\[ QT = \frac{1}{\epsilon} \ln \left( \frac{\zeta + v_r - v_{\text{min}}}{\zeta + v_r - 1} \right) \]

\[ RR - QT = \frac{1}{\epsilon} \ln \left( \frac{1 - v_r}{v_{\text{min}} - v_r} \right) \] (2)

We work in a regime where \( \zeta = 1.04, \lambda = 0.4 \) may be fixed according to Ref. (Idriss et al, 2012). This leaves \( \epsilon, v_{\text{min}} \) and \( v_r \) as fitting parameters. Applying an optimization procedure within the

singular limit has demonstrated a stiffness in the parameter \( v_r \), so we fixed \( v_r = 0.04 \) for all mice. Additionally, it should be noted that a global shift in \( v_r \) acts as a compression or dilation of

the overall scale in observed RoR values. The results of this analysis are essentially unchanged

as \( v_r \) is varied over a range 0.01-0.05. With only two unknowns in the system Eqs. (2), \( \epsilon \) and

\( v_{\text{min}} \) may be obtained by solving Eqs. (2) for each pair of QT and RR values using a numerical

root-finding procedure. The procedure of fitting is thus reduced to the solution of a two-variable

algebraic system. To relate the dimensionless RR and QT predictions to measurements, we

\[ \frac{c_m}{\sigma_{\text{Na}}} \approx 1 \] ms, so that

the dimensionless predictions are equivalent to measurements in milliseconds.
Armed with all system parameters, one may obtain the critical recovery current by applying the methods of Ref. [1] to obtain the value of $v_r$ for which wave propagation speed $c$ is maximized,

$$v_r = \frac{\varepsilon(1 - \zeta) + k_1^2(c) - \lambda}{\varepsilon + k_1^2(c) - \lambda} \cdot \frac{k_2(c)}{k_2(c) - k_1(c)}$$

$$k_1(c) = -\frac{c}{2} - \sqrt{\frac{c^2}{4} + \lambda}$$

$$k_2(c) = -\frac{c}{2} + \sqrt{\frac{c^2}{4} + 1}$$

This maximum value of $v_r$ is known as $v_{r,\text{crit}}$, and the RoR is defined as the normalized difference between the actual minimum in recovery current $v_{min}$ and this critical value $v_{r,\text{crit}}$. Fig. 1 shows a graphical depiction of the RoR, where $u(t)$, $v(t)$ are plotted with the actual $v_{min}$ and $v_{r,\text{crit}}$ indicated.
Figure 1: Simulated electrical excitations within the CSC model in the singular limit (see appendix). The variable $u$ corresponds to membrane potential. As the pulses become more narrowly separated, the minimum value attained by the recovery current $v$ rises. A critical value $v_r^{\text{crit}}$ exists for each set of parameters such that $v_{\text{min}} > v_r^{\text{crit}}$ corresponds to propagation instabilities, since the variable $v(t)$ must drop below $v_r^{\text{crit}}$ in order for stable propagation to occur. The $RoR$ uses QT and RR interval measurements to assess vulnerability by computing the normalized difference between $v_r^{\text{crit}}$ and $v_{\text{min}}$ using QT and RR intervals as inputs.

References
