Electronic Supplementary Material (ESI) for Environmental Science: Nano.

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

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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).

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

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

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

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:

$$QT = \frac{1}{\varepsilon}\ln\frac{\zeta + v_r - v_{min}}{\zeta + v_r - 1}$$

$$RR - QT = \frac{1}{\varepsilon}\ln\frac{1 - v_r}{v_{min} - v_r}$$

(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 ε, v_{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), ε and v_{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 multiply them by the ratio of membrane capacitance to sodium conductance $\frac{c_m}{\sigma_{Na}} \approx 1$ 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,

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

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

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

(3)

This maximum value of v_r is known as v_r^{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^{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^{crit} indicated.

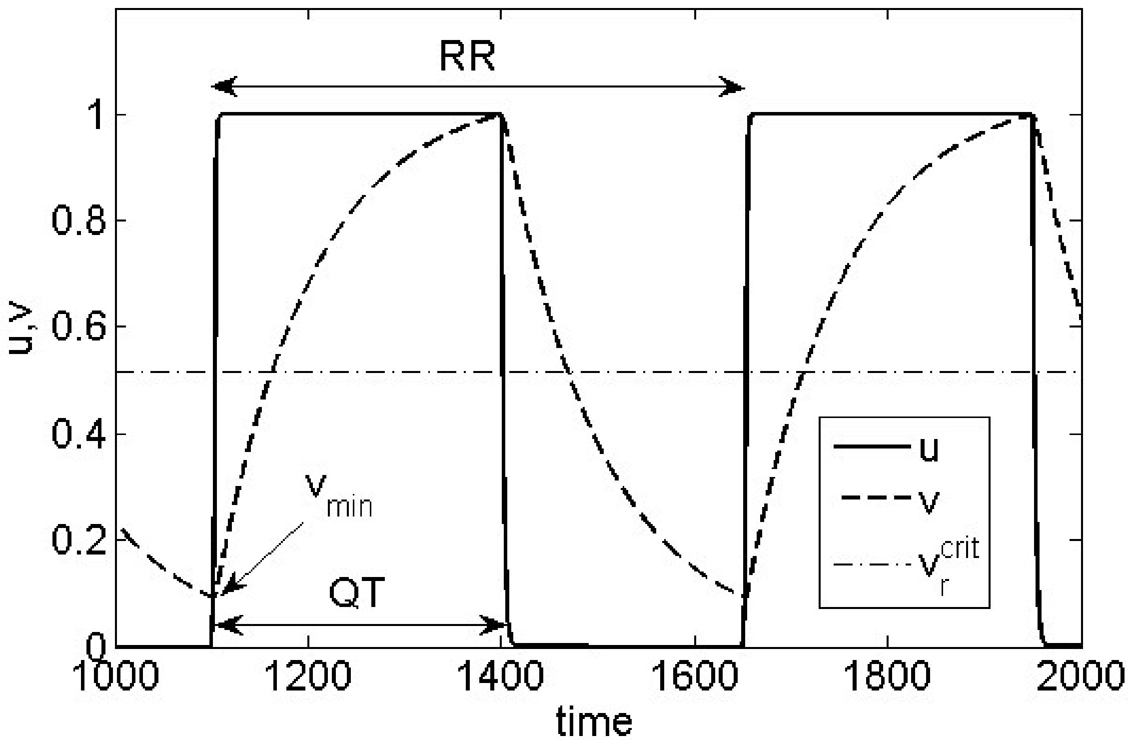

Figure 1: Simulated electrical excitations within the CSC model in the singular limit (see appendix). The variable u corresponds to membrane potential. As the pulses become more $v_r$narrowly separated, the minimum value attained by the recovery current v rises. A critical value v_r^{crit} exists for each set of parameters such that $v_{min} > v_r^{crit}$ corresponds to propagation instabilities, since the variable $v(t)$ must drop below v_r^{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^{crit} and v_{min} using QT and RR intervals as inputs.

References

1. Y.B.Chernyak, J.M.Starobin, R.J.Cohen. Class of exactly solvable models of excitable media, *Phys. Rev. Lett.*, 1998 **80**, 5675-5678.