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Cardio-Mathematics

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Modern toilets and cardiac cells have been famously likened to one another because of what they have in common: excitability. In the absence of electrical stimulus currents, the voltage $v$ across a cell membrane equilibrates to an asymptotically stable resting potential $v_{\text{rest}}$, much as the toilet remains in a resting state if its handle is not pressed. If either system is stimulated too weakly (sub-threshold electrical current or pressing the handle too lightly), the system relaxes rapidly to its rest state. Super-threshold stimulation causes a dramatic response known as action potential for cardiac cells and flushing in the toilet. Both systems eventually return to rest, but require time to recover excitability – briefly pressing the toilet handle (no matter how hard) during a flush does not elicit a noticeable response.

Understanding connections between the cardiac action potential and actual heart rhythm is not too difficult. Models of the action potential in a single cell take the form

$$C_m \frac{dv}{dt} + F(v,w) + I_{\text{stim}}(t) = 0, \quad \frac{dw}{dt} = G(v,w),$$

where $C_m$ is the capacitance of the cell membrane and $F: \mathbb{R} \times \mathbb{R}^n \rightarrow \mathbb{R}$, $(v,w) \mapsto F(v,w)$, represents a sum of the various currents which flow across the membrane. The vector $w \in \mathbb{R}^n$ describes the cell membrane's (variable) permeability to inward or outward current flow as modeled by $G: \mathbb{R} \times \mathbb{R}^n \rightarrow \mathbb{R}^n$, $(v,w) \mapsto G(v,w)$. The term $I_{\text{stim}}$ corresponds to an impulsive stimulus current supplied by the heart's native beating activity (more below). Choosing the functions $F$ and $G$ such that the system (1) is excitable and reproduces experimental data is an ongoing challenge. At the very least, there must exist an asymptotically stable rest state $(v_{\text{rest}},w^*)$ to which the cells would equilibrate, were it not for the occasional stimuli supplied by $I_{\text{stim}}$. Moreover, the equation $F(v,w) = 0$ should implicitly define a manifold $\Sigma$ in phase space forming an “excitability boundary” (see Figure 1).

The stimulus current can be thought of as a linear combination of $\delta$-distributions

$$I_{\text{stim}}(t) = \sum_j \mu_j \delta(t-t_j),$$

where $\mu_j$ is a stimulus strength (measured in microamps, no variation from beat-to-beat) and $t_j$ is the arrival time of the $j$th stimulus (i.e. the beginning of the $j$th heartbeat). Substituting (2) into (1) results in a system of impulsively forced differential equations. For information on impulsive DEs in a similar context see, e.g., [1]. The relationship between dynamics of (1) and the inter-beat intervals $\Delta t_j = t_j - t_{j-1}$ is of critical importance.

The stability of heart rhythm (or lack thereof) can be extracted from the impulsive DE model of the action potential. Let $v = v_{\text{APD}}$ denote a voltage above which we regard tissue as being “excited.” The hyperplane $v = v_{\text{thr}}$ partitions $(v,w)$ phase space into two regions, and a solution trajectory of the DEs crosses $v = v_{\text{thr}}$ twice during a typical beat: once as the cell is becoming excited ($\frac{dv}{dt} > 0$) and once as the cell is recovering excitability ($\frac{dv}{dt} < 0$). The difference between these two crossing times measures the action potential duration (APD), and we shall denote the APD of the $j$th beat by $A_j$. Using the planar $v = v_{\text{thr}}$ much as we would use a Poincare section to define a first return map, there exists a mapping $A_{j+1} = \phi(A_j, \Delta t_j)$ which recursively determines the sequence of APDs. This recurrence (known as the restitution mapping) and its higher-dimensional generalizations, can be used to study heart rhythm. In particular, if the stimulus times $t_j$ are evenly spaced with period $\tau$, the mapping $A_{j+1} = \phi(A_j, \tau)$ can suffer period-doubling bifurcations (the heart rate) is varied, leading to abnormal oscillations in APD.

Research at the interface of mathematics and cardiology can be doubly rewarding in the sense that problems of high clinical importance tend to spawn questions of independent mathematical interest, such as:

- How do the statistical properties of the sequence of stimulus times $t_j$ affect the dynamics of the DEs or the mapping $\phi$? Which, if any, cardiac abnormalities can be predicted or diagnosed by analysis of these sequences?
- What is the “best” way for a medical device to intervene by perturbing the sequence $t_j$ in such a way that normal rhythm is preserved/recovered?
- Beyond the cardiac context, can we prove new results about the dynamics of impulsively-forced excitable systems?

The article [2] surveys these and other research problems in “mathematical cardiology,” and the textbook [3] is an excellent starting point for mathematicians who are interested in applications to physiology.

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References

