From channels to systems: Ca^{2+}-sensitive K^+ currents, alternans and cardiac arrhythmia

Christopher L-H Huang, Physiological Laboratory and the Department of Biochemistry, University of Cambridge, Cambridge CB2 3EG, United Kingdom.

Key words: Ca^{2+}-sensitive K^+ channels, action potential alternans, restitution, arrhythmias

Short title: From ion channels to systems.

Correspondence to:

Christopher L-H Huang,
Physiological Laboratory,
University of Cambridge,
Cambridge CB2 3EG.
United Kingdom.
Email: clh11@cam.ac.uk
Phone: 01223 333822

Invited Editorial for: JP-RP-2016-273626XR1 "Dynamical effects of calcium-sensitive potassium currents on voltage and calcium alternans" by Matthew Kennedy, Don M. Bers, Nipavan Chiamvimonvat, and Daisuke Sato

Word count: article = 585 words; figure legend =137 words; 5 references.

Surface membrane ion channel function and its modification by intracellular, metabolic or Ca^{2+} homeostatic, conditions underlies both stable and pro-arrhythmic cardiac electrophysiological activity. Biophysical studies provide much understanding of the properties of specific channel types. However, in vivo action potential (AP) activation, propagation, and recovery reflect complex interconnected voltage-dependent interactions between multiple channels. These require study at the systems level beyond cell and molecular level analysis, either experimentally employing genetic or pharmacological manipulation, or by mathematical modelling, of cardiomyocytes, tissue segments or intact isolated hearts. Either approach seeks to demonstrate arrhythmogenesis at the systems level and then to resolve underlying cellular mechanisms in the corresponding model system.

An important computational study in this *Journal of Physiology* issue (Kennedy et al., 2017) investigated effects of the Ca^{2+}-activated, slowly activating delayed rectifier and small conductance potassium (SK) channels, respectively carrying I_{Ks} and I_{SK}, on pro-arrhythmic instabilities producing AP duration (APD) alternans. Such alternans can reflect membrane potential ($V_m(t)$) instabilities from steep dependences of APD restitution upon diastolic interval (DI) and are known clinically to presage major ventricular arrhythmias. Fig. 1A points out that decreasing steady-state *basic cycle lengths* (BCL) (*Aa*) reduces the DIs separating successive APs, since DI = (BCL-APD). This limits attainable heart rates as DI converges to the effective refractory period, ultimately causing 2:1 block (*Ab, Ac*: dotted lines). Alternatively, if APD varies with DI (*Ab, Ac*: continuous lines), attainment of unity slope in the resulting APD(DI) restitution curve (*Ad*: dotted tangent) predicts instability and APD alternans. Alternans can also accompany instabilities in intracellular calcium (Ca_i) cycling through steep dependences of sarcoplasmic reticular Ca^{2+} release upon Ca load/refractoriness (Groenendaal et al., 2014). Finally, interactions between Ca_i and K^+ channels also affect AP recovery: increased Ca^{2+} transients in given beats prolonging or shortening APD may positively or negatively couple V_m and Ca_i cycling.

The analysis integrated computational models for I_{Ks} and I_{SK} and their [Ca^{2+}] dependence into a physiologically detailed mathematical formulation of AP and Ca_i cycling in ventricular myocytes, extending the cellular representation into a mono-domain one-dimensional cable (Shiferaw et al., 2005). After first confirming that I_{SK} shortens APD, it explored stability boundaries for a baseline system before and following introducing I_{Ks} or I_{SK}. The latter caused a negative $Ca_i \rightarrow V_m$ coupling and negative ΔAPD vs ΔCa slopes leading to predictions of a succession from V_m-driven electromechanically concordant alternans, through Ca_i-driven electromechanically discordant alternans, to quasiperiodic oscillations capable of generating tissue level Turing-type instabilities. This confirmed previous experimental voltage and Ca^{2+} recordings.

The report thus clarifies contributions of Ca^{2+}-sensitive K^+ channels on *temporal* electrophysiological heterogeneities and their consequences for membrane stability as might be studied in recordings from single

cells (*Ae*). In future, this systems analysis could be extended to the corresponding *spatial* heterogeneities thereby potentially informing the increasing interest in experimental mapping studies of cardiac electrophysiological activity in both normal and arrhythmic hearts (Martin et al., 2011). Transforms of $V_m(t)$ (*Aa*), APD (*Ab*) and DI (*Ac*) mapped over *time*, *t*, giving APD(DI) restitution properties (*Ad*), could yield *spatial* representations over the tissue geometry, *x*, by introducing a conduction velocity term θ (*Ba*). The resulting $V(x)$ over space, *x*, yields active, λ (*Bb*), and resting AP wavelengths λ_0 (*Bc*) corresponding to wavefronts of electrophysiological AP excitation and recovery that together make up the respective *basic cycle distances* (*Ba*: BCD=$\lambda+\lambda_0$). The unity slope instability criterion in the resulting $\lambda(\lambda_0)$ plot (*Bd;* dotted tangent) now encompasses AP propagation in addition to recovery characteristics (Matthews et al., 2013), and offers one of many possible developments of this elegant approach.

Conflicts of interest: none declared.

Acknowledgements: CLH's work is funded by the Medical Research Council (MR/M001288/1), Wellcome Trust **(**105727/Z/14/Z), British Heart Foundation (PG/08/116), the McVeigh Benefaction and SADS UK.

References:

Groenendaal, W., Ortega, F. A., Krogh-Madsen, T., Christini, D. J., 2014. Voltage and calcium dynamics both underlie cellular Alternans in cardiac myocytes. *Biophys J* 106, 2222–2232.

Kennedy, M., Bers, D., Chiamvimonvat, N., Sato, D., 2017. Dynamical effects of calcium-sensitive potassium currents on voltage and calcium alternans. *J Physiol* In Press.

Martin, C. A., Guzadhur, L., Grace, A. A., Lei, M., Huang, C. L. H., 2011. Mapping of reentrant spontaneous polymorphic ventricular tachycardia in a Scn5a+/- mouse model. *Am J Physiol Heart Circ Physiol* 300, H1853–H1862.

Matthews, G. D. K., Guzadhur, L., Sabir, I. N., Grace, A. A., Huang, C. L. H., 2013. Action potential wavelength restitution predicts alternans and arrhythmia in murine Scn5a+/− hearts. *J Physiol* 591, 4167–4188.

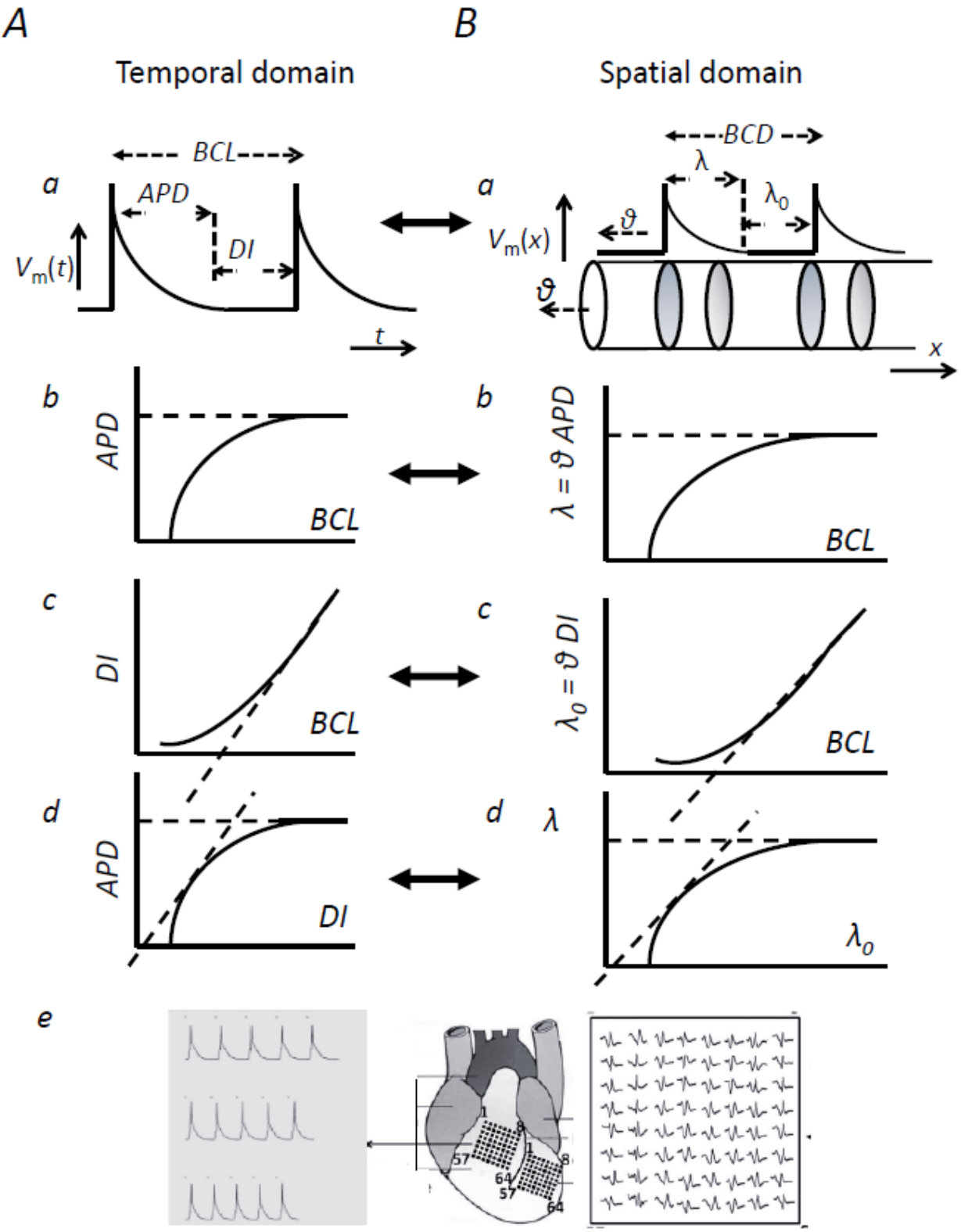
Shiferaw, Y., Sato, D., Karma, A., 2005. Coupled dynamics of voltage and calcium in paced cardiac cells. *Phys Rev E - Stat Nonlinear, Soft Matter Phys* 71.

Figure legend

Figure 1. Restitution analysis in the temporal and spatial domains.

(*A*) *Temporal* patterns $V_m(t)$ of cellular action potentials (APs), duration APD, over time, *t*, (*a*) with regular stimulation at progressively shortened basic cycle lengths (BCL) (*b*) with (continuous line) or without variations in APD (dotted lines) results in a corresponding dependence of diastolic interval (DI) upon BCL (*c*). Unity gradient of the resulting APD(DI) restitution function (dotted tangent) provides an instability criterion relating AP recovery characteristics to alternans (*d*). (*B*) Systems analysis additionally incorporating *spatial* AP propagation at velocity θ, generates active and resting wavelengths, λ, and λ_0 (a), each varying with BCL (*b*,*c*). Unity gradients in the derived $\lambda(\lambda_0)$ plots (*d*; dotted tangent) yield instability conditions that additionally incorporate AP propagation contributions. (*A, B*) thus constitute complementary temporal and spatial analyses of cardiac electrophysiological activity (*e*).

Figure 1


A
Temporal domain
B
Spatial domain
a
BCL
APD
DI
$V_m(t)$
t
a
BCD
λ
λ_0
ϑ
$V_m(x)$
ϑ
x
b
APD
BCL
b
λ = ϑ APD
BCL
c
DI
BCL
c
λ_0 = ϑ DI
BCL
d
APD
DI
d
λ
λ_0
e
1
8
57
64
1
8
57
64