

Supplementary Information

Data-extracted gating kinetics yield parameter-efficient, predictive models of four cardiac ion channels

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Companion to the main text. All numerical entries are transcribed from the sealed model cards and judgement cards of the channel lines; where a quantity is registered rather than sealed, its registration wording is preserved.

S1. Model equations and extracted tables

All four models share one construction rule: every voltage dependence is an extracted lookup table (log-linear interpolation: linear in V, logarithmic in the tabled quantity, endpoint clamping outside the measured range). There are no rate equations, no state topologies, no continuous spectra, and no parameter was obtained by global optimisation against the protocols used for validation. Model equations below are numbered (S1)–(S12); the model62 reference formulation equations are numbered (S13)–(S18).

S1.1 hERG (I_{Kr}). Sealed 2026-09-14

Equations. The gating variables obey

$$\frac{dm}{dt} = \frac{m_{ss}(V) - m}{\tau_m(V)},$$

$$\frac{dh}{dt} = \frac{h_{ss}(V) - h}{\tau_h(V)},$$

and the current is

$$I(t) = G m h (V - E_{rev}),$$

with $E_{\text{rev}} = -88.33$ mV and integration step $DT = 1 \times 10^{-4}$ s. Single gate m (B5 verdict) times single gate h .

Table S1.1a. Deactivation staircase time constants (s; sealed; engine anchors).

V (mV)	τ_f	τ_m (staircase middle mode)	τ_{late} (staircase slow mode)	single-gate engine τ_m anchor
−70	0.191	0.813	2.055	0.813 (TM)
−60	0.276	1.205	4.418	1.205 (TM)
−50	0.600 (ceiling-flagged)	1.800	10.14	10.14 (TAU_L)
−40	0.600 (ceiling-flagged)	0.800	24.05	24.05 (TAU_L)

Cross-cell CV 0.13–0.19. τ_f at −50/−40 hits the fit-band ceiling [0.03, 0.6] s; the fast/middle split is not identifiable within the window at these voltages (information limit, registered, not a model error).

Table S1.1b. Repolarisation-window recovery/deactivation (s; sealed, 4 levels).

V (mV)	−120	−110	−100	−90
τ_r (recovery; engine anchor)	0.00304	0.00425	0.00505	0.0065 (flagged)
τ_h				
τ_d (deactivation; engine anchor)	0.0303	0.0492	0.0858	0.072 (flagged)
τ_m				

Table S1.1c. Steady-state availability $h_{ss}(V)$, measured (12 carried levels, −70–+40 mV; −80 mV data-limited and registered; +50/+60 mV via endpoint policy).

V (mV)	h_{ss} median	CV	n	verdict
−80	0.798	0.21	3	data-limited (median

V (mV)	h_{ss} median	CV	n	verdict
				registered, P_2)
−70	0.425	0.26	6	sealed
−60	0.310	0.31	8	registered
−50	0.255	0.21	7	sealed
−40	0.208	0.24	7	sealed
−30	0.170	0.29	7	sealed
−20	0.137	0.32	7	registered
−10	0.114	0.37	7	registered
0	0.090	0.44	7	registered
+10	0.072	0.38	6	registered
+20	0.053	0.46	6	registered
+30	0.039	0.55	6	registered
+40	0.029	n/a	n/a	registered (QC3 vs R3-chain median 0.015, ratio 2.0 ∈ [0.3, 3]; engine +40 end uses R3 per- cell anchor)

Endpoint policy: P_1 anchors 1.0 at −100 mV and below; P_3 per-cell quality-controlled values with population-median fallback; P_4 (+50/+60) via the R3 chain. **B1 (h = 1 at negative voltages) is dead:** measured 0.425/0.310/0.255 at −70/−60/−50 mV.

Table S1.1d. $\tau_h(V)$ repolarisation segment (ms; τ_{obs} measured upper-bound medians, sealed 5/6 levels).

V (mV)	−70	−60	−50	−40	−30	−20	0/+60
τ_h	7.0	7.0	8.9	14.4	14.4	50	1.5

V (mV)	−70	−60	−50	−40	−30	−20	0/+60
						(bridge, registered ; sole remainin g bridge in the τ_h chain)	(instantaneous declaratio n)

Table S1.1e. Conductance G (nA/mV; nine cells; hook −120 anchor A/31.67, R1 fallback chain).

	167040	167040	167070	167080	167080	167081	167130	167131	167150
cell	07	47	14	16	60	18	03	10	49
G	0.1594	0.0718	0.0312	0.0980	0.0712	0.0253	0.1309	0.1611	0.0737
		*							

*flagged posthoc G_{inact} (D2).

Table S1.1f. Engine $\tau_m(V)$ anchors for $V \geq -40$ mV (s; registered slow-component medians).

V	+40/+5								
(mV)	−30	−20	−10	0	+10	+20	+30	0	+60
τ_m	9.8	4.0	2.8	2.0	1.2	0.71	0.45	0.29	0.30

Fast component (20–100 ms) does not enter the single gate m (B5 declaration). Activation delay 50–150 ms measured here from envelope-sigmoid feet, with voltage dependence $0 \rightarrow +40$ mV $\approx 10\text{--}15\times$; the delay’s existence and its mechanistic origin in two voltage-sensor steps are established in the literature (main-text ref. 21 and citations therein), and the present contribution is its quantification as a directly measured table in this dataset class. $m_{ss}(V)$ anchors use the re-split formula $\min(1, y_{ss}(V)/h_{ss}(V))$ with per-cell y_{ss} at −70/−60/−50 mV and registered logic bridges at −80/−40/−30 (B3 weakest bridge registered).

τ_{act} **registration band (not sealed; B6 target):** +40 mV: free median 131 ms / anchored 228 ms (CV 0.36, d- τ degeneracy dominant); 0 mV: median 1.73 s (range 0.6–4.8 s). Stage B sensitivity over the full band ($\times 0.3\text{--}\times 2$) is sealed: inter-arm V1 range 0.016 (S5).

B6 residual gap (registered): direct envelope measurement gives $m \approx 0.11 \cdot m_{\infty}$ at 100 ms of a +40 mV step; AP direct measurement requires $m \approx 0.29 \cdot m_{\infty}$; gap narrowed to 2.1–2.6 $\times$, H2 (cross-cycle accumulation in the AP train) the surviving main explanation, with quantitative prediction card on record (500 ms CL 2.36 $\rightarrow$ $\geq$ 1500 ms CL 1.00). Awaits new +50/+60 mV activation data.

S1.2 $Na_v 1.5$ (I_{Na}). Sealed 2026-09-15; final review revision 2026-09-16

Equations.

$$I = G m(t)^3 h(t) (V - E_{\text{rev}}),$$

$$\frac{dm}{dt} = \frac{m_{\infty}(V) - m}{\tau_m(V)} \quad (\text{apparent coordinates: command voltage, contains Rs artefact, registered}),$$

$$\frac{dh}{dt} = \frac{h_{\infty}(V) - h}{\tau_h(V)} \quad (\text{sealed core}).$$

All kinetics are cross-cell mean tables; per-cell free quantities are exactly G and $\Delta V_{1/2,h}$.

Table S1.2a. $\tau_h(V)$ inactivation time constants (ms; 35 °C; sealed).

V (mV)	−30	−20*	−10	0	+10	+20	+30	+40
τ_h	1.639	0.494	0.613	0.511	0.414	0.335	0.303	0.270

*−20 mV is an activation-foot protocol boundary (registered; value used, constancy not counted). −30 mV extension: CV 0.029 (sample CV computed from the full-precision per-cell values 1.634/1.594/1.688 ms, sealed-level). −10 $\rightarrow$ +40 monotone speed-up $\approx 2.3\times$ (apparent e-fold ≈ 60 mV, includes activation–inactivation coupling; no mechanistic reading).

Table S1.2b. $h_{\infty}(V)$: Boltzmann, $k_h = 4.79$ mV (sealed; per-cell 5.45/4.01/4.91, CV 0.15); $V_{1/2,h} = -66.1$ mV + Δ_{cell} with $\Delta_{\text{cell}} = +4.0$ (008), +0.1 (011), −4.2 (005) mV, a necessary per-cell parameter, magnitude consistent with cross-cell voltage zero-offset.

Table S1.2c. $\tau_m(V)$ activation (ms; apparent coordinates; registered, restricted).

V (mV)	-20*	-10	0	+10	+20	+30	+40
τ_m	0.075	0.0323	0.0262	0.0264	0.0251	0.0216	0.0216

-10 mV constant (CV 0.22, sealed); *-20 mV not constant (foot); $\geq +10$ mV: only an upper bound $\tau_m \lesssim 0.02$ ms is known (5 kHz chain resolution limit, registered).

Table S1.2d. $m_\infty(V)$: mean table $V_{1/2,m} = -35.2$ mV, $k_m = 3.67$ mV. **Not portable** ($V_{1/2,m}$ spread 11.8 mV; k_m CV 1.19; cross-compensation-level drift 19.1 mV): series-resistance residual artefact dominates, independently reproducing the artefact-model conclusion⁹. Used only in command-voltage coordinates (the C1 self-consistent forward, 3/3).

Table S1.2e. Remaining quantities. $E_{rev} \approx +72$ – $+75$ mV (registered: no reversal bracket, I–V fit, 2/3 cells at upper bound, weakly identifiable); $\tau_{deact}(-120\text{mV}) = 0.17$ – 0.29 ms (CV 0.34 boundary, 008 slower 1.8 $\times$); $G = 405 / 369 / 459$ pS (008/011/005).

Table S1.2f. $\tau_h(-40\text{mV})$: a distribution, not a value (N α -4, 69 patches). Median 1.03 ms; CV = 0.772; range 0.31–6.64 ms; τ correlates with late-current fraction ($\rho = 0.44$), marking modal-gating phenotype fluctuation. Mechanism corroboration (post-seal, registration-grade): the source study's own structural and functional analysis of the same recordings (main-text ref. 20) demonstrates that $Na_v1.5$ channels within a membrane patch do not gate independently: closed-state inter-channel interaction stabilises slow inactivation in a cluster-size-dependent manner (reduced late current and blunted use-dependent block in multi-channel patches), providing an independent physical basis both for the broad $\tau_h(-40)$ distribution registered above and for its correlation with late-current fraction ($\rho = 0.44$). Sealed verdicts are unaffected. Whole-cell values (1.64/1.68/3.15 ms) sit in the upper half of the patch distribution. **This level must not be cited as a single value.** The sealed domain -30–+40 mV is unaffected (sealing was based on mid-band CV ≤ 0.26). Activation arm (m gate) permanently closed to α -reconstruction: in the cell-attached reference the multi-channel τ_{decay} CV is 0.772 (the same $n = 69$ statistic cited immediately above; one statistic cited once per argument, not a second independent estimate) and the single-channel $P_{o,peak}$ CV is 0.602 ($n = 14$, 16 $\times$ spread) at -40 mV; I_{Na} retains the published ORd Markov form in the host assembly (decision given its hardest basis by N α -4).

Forward record: N α -1 τ_h constancy 6/7 (mid-band CV 0.05–0.26); N α -2 C1 NaIV full-trace forward 3/3 (RMS/peak 2.8/3.4/2.6% vs 8% line; mid-band per-level R^2 0.83–0.94); C2

availability forward 1/3 (011 $R^2 = 0.9983$; 008/005 fail on $\Delta V_{1/2,h} \pm 4$ mV, mechanism clear); controls S1/S2/S2b/S3 all pass (τ_m recovery 0.3%; Boltzmann $V_{1/2} \leq 0.25$ mV; self-consistency $R^2 = 1.000000$). $Q_{10}(314)$ 2/3 self-consistent (1.80/1.62/1.41, registered). Data gaps (registered): recovery $\tau_{\text{rec}}(V)$ (no recovery protocol in dataset); slow inactivation (1009 ms conditioning may contain slow components; h_∞ is apparent); true m_∞ (requires full clamp-dynamic modelling⁹); $\tau_m \geq +10$ mV (amplifier bandwidth).

S1.3 $Ca_v1.2$ (I_{CaL}). Component-level seal 2026-09-15

Sealed scope (declared): the two-input structure of the inactivation block + temperature policy + drug-module architecture. The full-channel forward model (full-voltage m_{ss}/τ_m tables, recovery branch) is **not assembled**; the gap is registered as a data requirement, not an omission (S6).

Equations (inactivation block, +17 mV anchor).

$$I(t) = G m(V, t) h(t) P(V),$$

with $P(V)$ the permeation factor (ramp chord G is a mixed quantity, see below). For Ba^{2+} (VDI skeleton, no CDI):

$$h_{Ba}(t) = 1 - f_{VDI}(1 - e^{-t/\tau_{\text{slow}}}),$$

and for Ca^{2+} (VDI skeleton plus CDI fast component, “add one term”):

$$h_{Ca}(t) = h_{Ba}(t) - w_{\text{fast}}(1 - e^{-t/\tau_f}).$$

CDI enters as a constant increment: not graded by current amplitude (Ca -2 negative), no two-dimensional $h_{ss}(V, Ca^{2+}_i)$: the “two-input” complexity collapses, at the experimental-design level (Ba^{2+} substitution), into a family of one-dimensional constants.

Table S1.3a. Inactivated fraction f_{inact} (+17 mV, 40 ms window; sealed family constants).

carrier	median	cross-cell CV	max/min	n
Ca^{2+}	0.73	0.141	1.52	6
Ba^{2+}	0.44	0.101	1.31	4

Protocol lock: values bind “+17 mV, 40 ms window, this external solution”; extrapolation requires re-measurement. $\Delta f(Ca - Ba) = 0.293$, CI90 [0.171, 0.392].

Cross-batch check (2026-09-21). The pre-drug control segments of 97 drug-screen cells in the same dataset (identical +17 mV, 40 ms convention) give f_{inact} medians 0.56 (Ca^{2+} , $n = 77$, CV 0.26, IQR [0.50, 0.77]) and 0.26 (Ba^{2+} , $n = 20$, CV 0.61): the characterization-batch values above sit at the upper quartile of the cross-batch distribution, and a strong protocol-variant dependence is visible (Verapamil-RT batch median 0.87). The sealed family constants are therefore batch-anchored: within-batch dispersion is small (CV 0.10–0.14) and cross-batch dispersion roughly doubles. All component-level contrasts used in this work (the CDI additive term, carrier-direction comparisons, pool-resolved drug effects) are same-batch or same-cell contrasts and are unaffected (verification card, 2026-09-21; S6 item (6)).

Table S1.3b. CDI fast component (group-level). $w_{\text{fast}} = 0.289$ (0.251–0.353 over separable cells), agreeing with $\Delta f = 0.293$ within 1.4%; $\tau_f = 6\text{--}12$ ms (12/8/6 ms over three separable cells); $\tau_{\text{slow}}(+17\text{mV}) = 50.0$ ms (Ca^{2+}) / 41.6 ms (Ba^{2+}), ratio $1.20 \in [0.7, 1.4]$ ✓; Ba^{2+} negative control 0/4. Cell-level stratification (registered): 3/6 separable (H1 wins, $\tau_f \leq 12$ ms), 3/6 inseparable (H1 hits $w = 0$ boundary; H0 mixed τ 24–39 ms), consistent with the identifiability boundary “ $\tau_f \gtrsim 14$ ms inside a 25 ms fit window”; adjudication requires ≥ 100 ms pulses at the same voltage (C α -3b suspended). Slow-VDI temperature anchor (descriptive): $\tau_{37} \approx 187$ ms, $Q_{10} \approx 1.94$ (single cell 0004, $R^2 = 0.774$, not judged).

Table S1.3c. Temperature policy (direct consequence of C α -4 verdict 1 ×). $Q_{10}(G)$ does not enter the constant tables: a chord-conductance temperature law exists (group medians Ca^{2+} 1.32 / Ba^{2+} 2.07, direction consistent with “12–34% decrease per 3 °C”) but is not a cross-cell constant family parameter (max/min above 2 in both groups; most per-cell regressions R^2 below 0.5). Treatment: temperature as an explicit covariate (bath temperature registered per cell per file); no uniform Q_{10} correction. Contrast with hERG (constant Q_{10} bridge passed): CaV temperature sensitivity is channel-specific, not a methodology failure.

Table S1.3d. E_{rev} and ramp chord conductance. $E_{\text{rev}}(\text{Ba}^{2+}) = +45.2 \pm 2.5$ mV (file coordinates; nominal $+28.2 \pm 2.5$), interpolation-level, sealed for use; $E_{\text{rev}}(\text{Ca}^{2+})$: this card gives lower bounds $+52.4$ (file) / $+35.4$ (nominal); the model retains the literature anchor $+46$ (nominal), the lower bound serving as consistency evidence. Ramp chord G is a mixed “permeation × residual gating” quantity (m_{∞} still rising inside the chord window [+30, +45] file) and is not interpreted as pure permeation conductance. Verdict 2 (carrier difference of E_{chord}) × but three lines of evidence point the same way (5/6 Ca^{2+} cells above all Ba^{2+} cells; Ca^{2+} a lower bound; Ba^{2+} within-group SD

2.5): “carrier difference strongly suspected, significance not sealed”; no post-hoc exclusion (pre-registered).

Table S1.3e. G and other. Per-cell free quantity: G only. Ba²⁺ group $G_{\text{med}} \approx 22$ -level; Ca²⁺ group ≈ 28 -level (0008 phenotype suspect 28.1, highest in group, registered). Activation kinetics (full-voltage $m_{\text{ss}}/\tau_{\text{m}}$): not sealed from this dataset (ramp segments mix activation information with gating; no single-extremum decomposition; S6 gap 1).

S1.4 I_{KS} (KCNQ1/KCNE1). Sealed 2026-09-15

Equations.

$$I_{\text{KS}}(t) = G a(V, t) (V - E_{\text{K}}),$$

$$a(V, t) = \beta a_{\text{ss}}(V) + (1 - \beta) a_{\text{dyn}}(V, t) \quad (\text{instantaneous} + \text{delayed two} - \text{component}),$$

$$a_{\text{ss}}(V) = \frac{1}{1 + e^{-(V - V_{1/2})/k}},$$

with $V_{1/2} = 25.05$ mV, $k = 22.6$ mV, $\beta = 0.30$ (pool constant, registered, not per-cell), and $E_{\text{K}} = -85$ mV (registered assumption, standard tsA201 solutions). Step segment: $t \leq d(V)$, $a_{\text{dyn}} = (1 - \beta) a_{\text{ss}}(V_{\text{pre}})$; $t > d(V)$, $a_{\text{dyn}} \rightarrow (1 - \beta) a_{\text{ss}}(V)$ as a single exponential with $\tau_{\text{act}}(V)$. Tail segment: a_{dyn} decays single-exponentially from its end-of-step value with $\tau_{\text{deact}}(V_{\text{tail}})$. The instantaneous component follows a_{ss} immediately.

Table S1.4a. $\tau_{\text{act}}(V)$ (s; author ground-truth table, Fedida 2024 data pack Zenodo 10421153, wt EQ; 22 °C, 10 s protocol; K α -2 verdict: simulations take this table preferentially; our 4 s protocol values are lower bounds. Post-seal source upgrade 2026-09-26 (K α -4): the earlier digitised version (Fig. 3B) was verified against this author table point-by-point, 25 points, relative error $\leq 2.2\%$ except the +180 mV endpoint (-10.5% , registered); sealed values below are the author truth.)

V (mV)	−60	−50	−40	−30	−20	−10	0	10	20	30
τ	2.02	2.67	3.55	3.65	8.59	8.91	7.66	5.69	4.30	3.60

V											
(mV)	40	50	60	70	80	90	100	120	140	180	
τ	2.91	2.48	1.92	1.64	1.42	1.35	1.02	0.80	0.50	0.29	

Bell-shaped: peak ≈ 8.9 s at -10 mV (author truth 8.912 s, $K\alpha$ -4). Linear interpolation, endpoint clamping. Cross-paper check ($K\alpha$ -2): $\tau_{\text{act}}(+60)$ 1.92 vs 1.491 s, ratio 1.29; both pass.

Table S1.4b. Delay $d(V)$ (s; author ground-truth table, Fedida 2024 data pack Zenodo 10421153. Post-seal source upgrade 2026-09-26 ($K\alpha$ -4): replaces the earlier Fig. 3C digitisation ($1.17 \rightarrow 0.31$ s), which read systematically low by 56–191 ms beyond the declared ± 0.1 s at $\geq +30$ mV, registered. The sealed ORd/CiPA runs used the digitised table; the upgrade shifts activation onset by ≤ 0.19 s, direction-neutral on all sealed verdicts, re-run not triggered, registered.)

V													
(mV)													
)	−20	−10	0	10	20	30	40	50	60	70	80	90	100
d	1.35	1.35	1.23	1.07	1.01	0.92	0.86	0.69	0.66	0.58	0.50	0.44	0.42

Endpoint clamping: below -20 mV $\rightarrow 1.35$ s; above $+100$ mV $\rightarrow 0.42$ s. Physical identity ($K\alpha$ -5): $d(V)$ is the voltage-sensor/pore concerted-step time constant $\tau_2 = 1/(\delta + \gamma)$ measured independently by VCF F2 fluorescence in the same study; d/τ_2 median ratio 0.89 (range 0.79–1.00, five voltages).

Table S1.4c. G-V and pool. $V_{1/2} = 25.05$ mV (Chan anchor 25.4, zero deviation, $K\alpha$ -1 verdict 0); $k = 22.6$ mV (methodological footnote: isochronal normalisation vs Chan peak-tail convention systematically shallower $\approx 16\%$, registered). Per-cell G: 5.2–29.1 (expression amplitudes 201–1087 pA); only G free per cell.

Table S1.4d. $\tau_{\text{deact}}(-40\text{mV})$: gap registration (citation discipline: “apparent value rejected; absolute magnitude anchored; per-cell spread real”, never “ I_{KS} deactivation unknown” or “deactivation failed”). Apparent $\tau_{\text{app}} = 0.40$ s ($K\alpha$ -1 extraction, CV 8.5%): decisively rejected in forward prediction ($K\alpha$ -3 arm A 0/8), demoted to an extraction-layer apparent quantity that does not enter the model. Absolute magnitude 2–3 s direction-anchored ($K\alpha$ -3 arm B df-difference 0.02–0.31, two cells passing both criteria; $K\alpha$ -1 in-window decay estimate 1.5–3 s

consistent). Single-value unification failed (arm B 2/8): per-cell spread real (consistent with $K\alpha$ -1 verdict 2 total CV 0.313). ORd assembly treatment: $\tau_{\text{deact}}(-40) = 2.0 \text{ s}$ + sensitivity arm (or per-cell free), registered as an I_{KS} -specific difference; all other voltages data-free, full table registered missing. Temperature: 22 °C single point; the 22→37 °C Q_{10} bridge is a registered gap (ORd stage used literature $Q_{10} \approx 2\text{--}3$ as sensitivity arm).

Forward record: activation-segment $R^2 \geq 0.80$ in 7/8 cells (7/7 excluding the registered boundary); instantaneous-component reproduction 0.062 vs 0.10 line.

S1.4e. Mechanistic identity of the extracted quantities and gold-standard pipeline test (post-seal, 2026-09-26; $K\alpha$ -4/5/6; source: Fedida 2024 data pack, Zenodo 10421153). (i) *Physical identity*. The delay $d(V)$ is the concerted voltage-sensor/pore second transition, not a fitting degree of freedom: VCF F2 fluorescence in the same study gives $\tau_2 = 1/(\delta + \gamma)$ per oocyte, and d/τ_2 has median ratio 0.89 (range 0.79–1.00) across five voltages. The bell-shaped $\tau_{\text{act}}(V)$ is the whole-path rate-limiting current rise, $\approx 7\times$ slower than τ_2 ; the two time scales have distinct mechanistic referents and are not redundant exponentials. (ii) *Apparent charge and validity window*. Limiting-slope measurements (recomputed per cell from the data pack, matching the published Table 3 to three significant figures) give true gating charge $z_a = 2.07\text{--}2.47 e_0$ for I_{KS} constructs and $6.08 \pm 0.30 e_0$ for hERG ($n = 4$); the single-Boltzmann apparent charge $z = RT/Fk$ (1.1–1.9 e_0 for I_{KS} ; ≈ 3.4 for hERG) undercounts z_a by a factor 1.3–1.8 in both channels, same direction. This is the structural cost of the single-variable a_{ss} reduction, not a fit failure. The valid window of a_{ss} is registered as $P_0 \gtrsim 0.01$; below it, allosteric access to multiple open states (the downward bend of the experimental limiting-slope plot) lies outside the α claim, consistent with the pre-existing low- P_0 no-claim boundary. (iii) *Gold-standard pipeline test*. The extraction pipeline was run unmodified on the data pack's Scheme V two-tier allosteric model currents (ground truth known). Recovery: G-V (conductance convention) $V_{1/2} = 14.1 \text{ mV}$ vs experimental isochronal 13.2 mV (0.9 mV); delay ratio median 1.06; τ_{act} ratio 0.9–1.1 at $V \geq +30 \text{ mV}$, with the low-voltage deviation traced (power-scan diagnostic) to the model's own kinetics, not to the extractor; the pipeline does not fabricate slow time constants absent from the traces. Single-exponential-plus-delay approximation error on allosteric traces: relative RMS 0.7–4.5%, largest at low voltages. Two convention lessons are registered: conductance must divide out the driving force (normalised-current convention manufactures a spurious 23 mV $V_{1/2}$ shift on the same traces), and the isochronal-to-equilibrium right shift (6.6 mV here) is slow-activation physics, so cross-study $V_{1/2}$ comparisons require matched isochronal conventions.

S2. Constancy judgement statistics and forward-prediction scoring

Verdict classes. Every extracted table receives one of four pre-registered verdicts before any held-out prediction: *constant* (carried as a channel-level table), *per-cell* (carried as a per-cell coordinate), *distributed* (carried as median + measured dispersion), *unusable* (excluded with named artefact). Verdicts are fixed prior to prediction and archived as judgement cards; no verdict was revised after seeing a forward score.

Constancy test. For a table entry x measured on n cells, the cell-to-cell coefficient of variation CV is compared against the measurement-noise CV estimated from within-cell replicate dispersion (protocol-specific; e.g., exponential-fit covariance for τ entries). The entry is declared constant when the two are statistically indistinguishable at the pre-registered level (variance-ratio F test, two-sided, $\alpha = 0.05$, with the additional operational requirement $CV \leq 0.30$ for family-constant registration). Boundary cases are registered with their CV and n rather than forced (e.g., hERG h_{ss} levels with $n \leq 3$; Nav $\tau_h(-40)$ with CV 0.40 across the three whole cells, later resolved as a 69-patch distribution, S1.2f).

Forward-prediction scoring. Pre-registered accuracy lines per channel: - hERG sinusoidal forward: per-cell trace-level error within the sealed tolerance in $\geq 7/9$ cells (observed 7/9; both failures data-side and on record: cells 047 and 060, S6). - hERG action-potential-clamp forward: $\geq 7/9$ (observed 8/9; sole failure cell 014 registered model-side: its h tables sit at the population median, individual deviation not captured). - hERG CiPA third-party reproduction: pimozi-subtraction pool (69 cells assembled, 35–37.5 °C; one signal-insufficient cell excluded, registered) reproduced in 65/68 (lab3 20/20; lab4 16/16; lab5 29/32); Q_{10} and E_{rev} sensitivity checks all pass and do not depend on bridge values. - hERG deactivation residual whiteness: Ljung–Box-type test on forward residuals of the deactivation staircase, pass 28/33 tail segments. - $Na_v1.5$ full-trace forward: $RMS/peak \leq 8\%$ (observed 2.8/3.4/2.6%). - I_{Ks} activation forward: $R^2 \geq 0.80$ per cell (observed 7/8; 7/7 excluding the registered boundary cell); instantaneous-component reproduction error ≤ 0.10 (observed 0.062).

Control batteries. Each line runs protocol-shape controls before scoring (e.g., Nav: τ_m recovery 0.3%, Boltzmann $V_{1/2}$ recovery ≤ 0.25 mV, forward self-consistency $R^2 = 1.000000$; hERG: observation-chain modal-expansion FIR identical to the sealing method). Failure of any control voids the run before judgement.

Registration discipline for failed cells. Forward failures are attributed data-side or model-side in the judgement card with evidence (e.g., hERG 060/016 baseline shift above $3 \times \text{MAD}$, 0.005–0.01 nA, 2–13% contamination of small inactivation currents, the h-chain break mechanism; hERG 014 model-side as above). Attributions are part of the sealed record (S6).

Independent population panel (Lei 211-cell CHO dataset, 25 °C; ref. 17). The same modal quantities were extracted under a pre-registered judgement card (frozen before any run; four pre-run amendments archived) from 211 automated-QC cells and, in parallel, the authors' 124-cell manually curated subset. Verdicts: per-cell E_{rev} *constant* (median -83.9 mV, CV 0.024, $n = 209$; subset -84.1 mV, CV 0.017); h_{ss} *constant* at $-140/-120$ mV (1.000/0.955, CV ≤ 0.065), registration-grade at $-60/+40$ mV (small-signal limb, CV 0.35–2.3); m_{ss} *constant* at $+25/+40$ mV (0.623/1.000, CV ≤ 0.22), registration-grade below $+10$ mV (1 s apparent activation at 25 °C = lower bound); deactivation slow components registration-grade (0.74 s at -60 mV, 3.03 s at -40 mV; ladder ordering preserved); recovery time constants registration-grade (4.3–16.8 ms over $-140/-20$ mV); activation/inactivation at $+40$ mV from the staircase big step (432 ms / 90 ms, registration-grade). AP-clamp forward (per-cell G , E_{rev} carried; population tables otherwise): A2 magnitude 191–206/209 per frequency (subset 124/124 at all three frequencies), rebound-peak ratio median 0.84 (subset 0.81), A3 frequency ordering 209/209 (subset 124/124); A1 per-cycle rebound criterion 77/209, 53/209, 157/209 at 0.5/1/2 Hz, combined 45.8% (Wilson 95% CI 42–50%; subset 59.1% [54–64%]), registered, not sealed. Stated limitations of this panel: (i) the 1.0 s activation pulses do not reach steady state below -20 mV at 25 °C; (ii) the h_{ss} statistic carries a $+10$ – 30% isochronal bias where recovery and deactivation race ($-100/-20$ mV; synthetic-recovery control voids the statistic at those voltages, pre-registered rule); (iii) the automatic leak correction required the authors' re-leak step (pivot -80 mV), which partially absorbs early activation current and voids activation-rise τ_{act} extraction; activation kinetics were therefore sourced from staircase step transients; (iv) the per-cycle rebound criterion ($\geq 80\%$ of cycles) is structurally stringent at 2–4 cycles per sweep (0.5/1 Hz), where one marginal cycle fails a cell; magnitude- and direction-based criteria pass at 96–100%. A 124-cell curated-subset re-score of every verdict reproduced or tightened all sealed entries (direction of effect as expected from manual QC), so population conclusions are robust to the QC convention.

Five-temperature Q_{10} layer and 37 °C cross-platform check (Lei temperature series; ref. 18). Five further batches (127 wells at 27 °C, 118 at 30 °C, 109 at 33 °C, 69 + 36 at 37 °C) were extracted with identical code under a separately frozen pre-registered card; no line was revised after the run. At 37 °C (two batches merged, $n = 105$) the population signatures replicated: E_{rev}

constant (-92.0 mV, CV 0.031, $n = 102$; the $25\text{ }^{\circ}\text{C} \rightarrow 37\text{ }^{\circ}\text{C}$ shift $-83.9 \rightarrow -92.0$ mV ends within 1 mV of the model62 reference formulation's fitted -92.9 mV (S3.0; an independent convention, pre-registered as not mutually binding)), h_{ss} *constant* at $-140 / -120$ mV (1.000/0.968, CV ≤ 0.06), m_{ss} *constant* at $+25/+40$ mV (0.900/1.000, CV ≤ 0.12); the deactivation-ladder direction was not established (slow component 0.27–0.30 s against the 0.5 s staircase window; window-limited, registered). AP-clamp forward at $37\text{ }^{\circ}\text{C}$: magnitude 79–98% per frequency, rebound-peak ratio medians 0.40–1.15, frequency ordering 100/102, combined per-cycle criterion 32.0% (Wilson 95% CI 27–37%), registered for the same structural reason as at $25\text{ }^{\circ}\text{C}$. Cross-platform absolute check at $37\text{ }^{\circ}\text{C}$: CHO median $\tau_{rec}(-120\text{mV}) = 1.52$ ms versus the construction-set sealed reference 3.04 ms, ratio 0.50 inside the pre-registered [0.3, 3] band: *sealed*. Q_{10} layer (population medians, five temperatures): $\tau_{rec}(-140/-120\text{mV})$ $Q_{10} = 2.84$ with log-linear $R^2 = 0.991$, *sealed*; big-step $\tau_{act}(+40)/\tau_{inact}(+40)$ endpoint $Q_{10} = 1.50/1.83$, *sealed* at the endpoints, Arrhenius linearity not established (grid-quantised plateaus at $27\text{--}33\text{ }^{\circ}\text{C}$, one non-monotone midpoint; registered); slow-deactivation $\tau_2(-40\text{mV})$ $Q_{10} = 7.6$, out of band (registered; window-limited at $37\text{ }^{\circ}\text{C}$ and non-monotone at $27\text{ }^{\circ}\text{C}$); $E_{rev}(T)$ slope $-0.58\text{ mV}/^{\circ}\text{C}$ (five-temperature regression value; the endpoint difference $-83.9 \rightarrow -92.0$ mV over $12\text{ }^{\circ}\text{C}$ corresponds to $-0.68\text{ mV}/^{\circ}\text{C}$ and is listed separately from the regression slope), direction Nernst, steeper than the pre-registered band (registered). Extraction-resolution check of the τ_{rec} Q_{10} (post-seal verification layer, 2026-09-21): τ_{rec} is extracted on a 22-point logarithmic grid (23% step; the striped appearance of the hERG τ_{rec} groups in Extended Data Fig. 8c is this extraction resolution, not a data artefact). A correctly seeded continuous re-refinement of all 1,340 fits at $-140/-120$ mV (median SSE improvement only 1.7–4.1%, i.e. the per-cell likelihood valley is nearly flat) shifts the five-temperature medians by $\leq 9\%$, except the resolution-censored $37\text{ }^{\circ}\text{C}$ -140 mV group ($1.23 \rightarrow 1.57$ ms; 55% of cells sit in the two lowest grid bins); re-refined $Q_{10} = 2.26$ (-140 mV, $R^2 = 0.970$) and 2.89 (-120 mV, $R^2 = 0.999$), and three model-free rise clocks (t_{10-90} , time-to-extremum, t_{half}) independently give $Q_{10} = 2.1\text{--}3.8$ ($R^2 \geq 0.985$). The sealed grid value 2.84 lies inside this band and is therefore not a grid-quantisation artefact; the $37\text{ }^{\circ}\text{C}$ -140 mV point is resolution-censored (registered). An earlier mis-seeded refinement variant (amplitude seeded with wrong sign) produced a spurious flat $Q_{10} \approx 0.9$ and was discarded; both variants are documented in the archived verification card. Per-temperature medians, CVs and verdict grades for every voltage are tabulated in the archived time table (Extended Data Fig. 6). A direction note on $h_{ss}(-120\text{mV})$: the measured values are 0.955 at $25\text{ }^{\circ}\text{C}$ ($n = 201$) and 0.968 at $37\text{ }^{\circ}\text{C}$ ($n = 105$), i.e. slightly less steady-state inactivation at the higher temperature. The direction is a property of the measured per-cell distributions (every contributing value is carried in the

master table, S7), not an artefact of pooling; it is reported as measured, with no mechanistic claim attached.

S3. Identifiability analysis of a 13-parameter Markov formulation

S3.0 Provenance and mathematical form of the model62 reference formulation

Status. model62 is our own interim hERG construction (frozen 2026-09-10, “181 endpoint”), documented in the deposited model card (2026-09-11). It is not a delivered product of this work and is not claimed to be a good model. It serves here in exactly two roles: (i) the object of the Fisher-information analysis of S3, as a representative of the globally fitted Markov-formulation class; and (ii) an independent-convention reference for two registered comparisons (the fitted reversal potential -92.9 mV at 37 °C, S2; the $+40$ mV engine anchor chain, S1.1). Its components are literature parts reassembled, and its known defects are documented below and in the archived model card.

Assembly. A four-state cyclic scheme (states 1-2-3-4-1, state 3 open; ring topology of the F11 2011 lineage) with opposite-edge equal-rate constraints ($k_{12} = k_{43}$, $k_{21} = k_{34}$, $k_{41} = k_{32}$, $k_{14} = k_{23}$), so that detailed balance holds by construction and only four rates are independent. The activation edge is bi-exponential (the second component follows the Wang 2013 two-charge mathematical form). In parallel with the ring conductance sits a slow component (X) gated at negative potentials. Occupancy dynamics: $dy/dt = M(v)y$ with y_4 eliminated; protocol voltage applied point by point; the fitting side integrates by Crank-Nicolson at 0.05 ms and the verification side by matrix exponential at 0.1 ms, with a bit-identical cross-check on record.

Rate equations (v in mV; rates in ms^{-1}):

$$k_{43}(v) = P_1 e^{P_2 v} + p f_1 e^{p f_2 v}, \quad k_{34}(v) = P_3 e^{-P_4 v},$$

$$k_{32}(v) = P_5 e^{P_6 v}, \quad k_{23}(v) = P_7 e^{-P_8 v}.$$

Slow component: steady state

$$x_{\infty}(v) = \frac{X_{\text{MAX}}}{1 + e^{-(v-V_H)/K_X}},$$

time constant

$$\tau_x(v) = \text{TAU0} \alpha_{\text{tau}} e^{Z v},$$

negative-potential gate

$$g_x(v) = \frac{1}{1 + e^{(v - \text{GX_MID})/\text{GX_K}}}$$

(73% conducting at -120 mV, 12% at -90 mV). Total current:

$$I(v, t) = [\text{GKr } y_3 + \alpha_{\text{amp}} \text{ALPHA } x_s g_x](v - \text{EREV}),$$

with $\text{EREV} = -88.33$ mV a Nernst value (K_i 130 / K_o 4 mM, 21.3 °C), not fitted; the α -model of S1.1 inherits this number.

Parameters. Sixteen slots, 13 free + 3 frozen ($\text{GX_MID} = -110$ mV; $\text{VH} = -50$ mV; $\text{KX} = 13.2$ mV), plus four legacy constants inherited from the preceding calibration card ($\text{XMAX} = 0.180967$; $\text{TAU0} = 3.97337$; $Z = 7.6390 \times 10^{-3}$ mV $^{-1}$; $\text{ALPHA} = 7.4761 \times 10^{-2}$). Free values at the 181 endpoint: $P_1 = 1.3073 \times 10^{-4}$; $P_2 = 5.6794 \times 10^{-2}$; $P_3 = 1.4718 \times 10^{-5}$; $P_4 = 6.3739 \times 10^{-2}$; $P_5 = 2.8136 \times 10^{-1}$; $P_6 = 2.1038 \times 10^{-2}$; $P_7 = 9.4491 \times 10^{-3}$; $P_8 = 2.6799 \times 10^{-2}$; $\text{GKr} = 0.12868$ μS ; $pf_1 = 9.0621 \times 10^{-5}$; $pf_2 = 5.9008 \times 10^{-2}$; $\alpha_{\text{amp}} = 0.65007$; $\alpha_{\text{tau}} = 0.44018$.

Calibration and known defects. Fitted on Beattie cell 16713003 over four protocols (steady activation, deactivation, sine wave, action-potential clamp). Self-set acceptance lines: 7 of 8 passed; the sine-wave R^2 of 0.95404 misses its 0.955 line by 0.00096 against a measured data ceiling of $R^2 \geq 0.973$, an architecture-level shortfall rather than noise. Nine-cell cross-validation (all 16 parameters fixed, only GKr re-scaled per cell) fails: only the calibration cell passes (5 of 6 lines), the other eight cells pass 1-4 of 6, so the parameter set is valid for the calibration cell alone and cannot be carried across cells. A candidate serial-closed-state extension was tested and found unidentifiable (Cramér-Rao bounds ± 9.6 -13.2 dex against a data-active window of ± 0.017 dex) and was not admitted. The full record is deposited (model card 2026-09-11; archive zip containing the 181 minimal run package).

Object. A 13-parameter Markov-type hERG formulation from our own interim modelling chain (the model62 reference formulation; provenance, equations and calibration record in S3.0), parameterised by global fit over the four hERG protocol families (activation, inactivation, deactivation staircase, sinusoidal). The analysis asks which combinations of the 13 parameters the data constrain.

Fisher information. The Fisher information matrix F was computed at the fitted point by automatic differentiation of the Gaussian log-likelihood over all four protocol families, with

observation noise estimated from per-sweep residuals. Eigendecomposition gives condition number $\chi = \lambda_{\max}/\lambda_{\min} = 7.4 \times 10^{12}$ with six near-null eigendirections (λ below the noise-equivalent threshold).

Exact degeneracies. Two null directions are exact algebraic degeneracies, verified symbolically: (i) a joint rescaling of all forward/backward rate constants by factor s together with conductance by $1/s$ leaves every protocol prediction invariant (rate–conductance joint scaling); (ii) the three parameters α_{amp} , ALPHA, XMAX enter the model only through their product $\alpha_{\text{amp}} \cdot \text{ALPHA} \cdot \text{XMAX}$, so the two-dimensional fibre holding the product fixed is unconstrained. Double-exponential component degeneracy (interchange of fast/middle branches) accounts for further near-null curvature.

Modal coordinates. Projection of F onto its non-null subspace recovers a coordinate system whose entries are precisely the quantities the extraction pipeline measures directly: activation/inactivation/deactivation time constants at the probed voltages, steady-state levels, and delays: the modal coordinates. The mapping from rate constants to modal coordinates is many-to-one along null directions: in a loop-inversion test, 0 of 451 attempts to invert modal coordinates back to the generating rate-constant point succeeded (samples drawn on the null manifold all reproduce the same modal coordinates).

Practical consequence. Rate constants quoted from such fits carry at least an order-of-magnitude ($\approx 10\times$) uncertainty along null directions; model cards in this work therefore quote only modal coordinates, with measured cell-to-cell dispersions (main text, Fig. 3a). Order-of-magnitude cross-cell stability of the modal ordering itself: 0.074 dex.

Slow-memory analysis (bounds of any memoryless table model). At identical voltage, hERG currents differing only in voltage history differ by factors of 17–112 (9/9 cells). The memory spectrum is continuous from 4.8 s to beyond 2,000 s. The present models capture the dominant discrete modes (fast/middle/late components, S1.1) and explicitly do not claim the continuum; this boundary is stated in the model cards and bounds the accuracy of any Hodgkin–Huxley-form reduction.

S4. Drug-action metrics and component attribution

Two shape metrics. For each drug and channel, control and drug segments of the same cell are compared in a ramp window after normalisation: - ε_x : cross-protocol discrepancy under a pure-

conductance-block model (single rescaling of G). hERG acceptance threshold 0.030 (noise floor 0.004; signal 20 $\times$). $Ca_v1.2$ threshold 0.139 = max(null-B p90, 0.03). - κ^* : steady-state shape deviation under a single-scalar rescaling after allowing a temporal warp; $|\kappa^* - 1|$ against threshold 0.10, with the fraction of deformation absorbed by warping reported separately.

hERG (whole-library run; 136/136 datasets judgeable, 517 cell-units). Pure block rejected: median $\varepsilon_x = 0.088 > 0.030$; concentration drift $\rho = 0.387$ ($p = 3.1 \times 10^{-20}$); 30/30 drugs above the line individually (median range 0.036–0.210; mexiletine strongest, vandetanib cleanest); relaxing the threshold to 0.08 leaves the conclusion unchanged. Deformation attribution: amplitude-shape dominates. Of the judgeable 440 units, median $|\kappa^* - 1| = 0.020$; warp absorbs only $\approx 15\%$ of deformation; residual $\varepsilon_{x1} = 0.075$ is still above the line. **Drug module pinned: coupling through h (h_{ss} modulation); τ tables unmoved.** Registered: κ^* rises slightly with concentration ($\rho = 0.39$), a small temporal component below the judgement line; dofetilide deformation almost purely amplitude-type ($f_{\tau} = 0.065$); concentration–time confound under incremental dosing registered (resolution needs washout/variant-protocol data).

Binding kinetics (hERG library base). dofetilide obeys single-step bimolecular binding ($k_{on} = 1.17 \times 10^{-4}$ /nM/s; $k_{off} = 5.29 \times 10^{-3}$ /s; $R^2 = 0.781$); pimozone does not ($R^2 = 0.507$), indicating multi-step or state-dependent binding; both drugs show trapped-type state preference (negative voltages do not relieve block; $b(-)/b(+)$ medians 0.92–2.91), consistent with inactivated-state preference coupling through the h gate. Perfusion-rate-limit rejected for two slow drugs (E-4031 same-cell reference $R_E = 3.4/9.0$): measured slow rates are genuine binding kinetics. Library-wide parameter base: 136 datasets, L1 anchoring 124/136 = 91.2% (9 of 12 failures in lab5, weak-blocker Hill ill-posedness); per-drug $\times$ lab $\{IC_{50}, n_H, k_{obs}(C), R_E\}$ panorama sealed; extraction pipeline cross-validated against laboratory anchors (IC_{50}/n_H ratios within [0.7, 1.4], four ratios 0.98–1.02; sweep-wise correlation median $r \approx 0.999$).

$Na_v1.5$. Pure block rejected; dual-component action: amplitude plus temporal term, $|\kappa^*| = 0.20$, quantitatively consistent with measured use dependence ($\Delta f = +0.12$). External benchmark panel: all seven computable comparisons fall within a $\pm 50\%$ band (verdict wording: the remaining comparisons are 3-point-insufficient, not IC_{50} mismatches).

$Ca_v1.2$ (139 files $\rightarrow$ 98 valid drug-cells, 8 drug groups). Pure block rejected: median $\varepsilon_x = 0.223 > 0.139$; 93% of cells above own-control drift; paired Wilcoxon $p = 7.2 \times 10^{-16}$; all 8 drug groups $\geq 80\%$ (Norbu- Ca^{2+} , Norbu- Ba^{2+} , Naloxone 100%). Amplitude-type modulation: κ^* median -0.01 ; warp absorbs only 2.7% of deformation: drugs change “how many channels are

available and how deep apparent inactivation is”, not time constants. State-specific shape modulation (verdict-3 citation discipline: “the pre-registered pool-classification hypothesis (inactivated-preference deepening + open-state neutrality) does not match measurement”, never “CDI/state-dependence evidence weak”): inactivated pool (verapamil $\times 2$ + diltiazem, $n = 43$) Δf median +0.168 (38/43 positive, binomial $p = 1.2 \times 10^{-7}$); open pool (norbuprenorphine- Ca^{2+} , $n = 12$) Δf median -0.088 ($|\text{median}|$ 0.143 above the zero-drift p_{90} 0.087), opposite directions, stronger state-specificity than expected. Carrier cross-validation (shape-level reproduction of the source paper): norbuprenorphine Ca^{2+} $\Delta f = -0.09$ vs Ba^{2+} +0.39 (same drug, opposite signs across carriers; paper: Ca^{2+} no difference, Ba^{2+} 2.4 $\times$); Ba^{2+} -group ε_x systematically larger (0.43–0.45 vs Ca^{2+} 0.11–0.33), corroborating “ Ba^{2+} enhances state preference”. External comparison 4/5 pass (vp-Ca-PT 1.66 $\checkmark$; vp-Ba-PT 2.03 $\checkmark$; norbu-Ca-PT 0.91 $\checkmark$; dilt-Ba-PT 1.43 $\checkmark$; vp-Ca-RT abstained, insufficient sample). Calibration targets for next-stage fitting: Δf medians verapamil-Ca-PT +0.13, diltiazem-Ba +0.41, methadone +0.20, norbu-Ca -0.09 . Registered: nominal concentrations unavailable (no dose–deformation relation); methadone facilitatory cells (facil flag) mixed into the main pool, its $\varepsilon_x = 0.33$ a bidirectional mixture.

I_{KS} . Multi-table modulation: batch-dependent shift of the activation steady state a_{ss} , instantaneous component +0.30, and deactivation suppression; the DIDS condition is pool-confounded in the source data and is reported as such (no ticket), not forced through the schema. Robustness check (2026-09-21): the 15 Mef-arm files extracted with the same pipeline give G-V fits of equal quality (median $R^2 = 0.994$), 15/15 sign-consistent instantaneous elevation (median $\Delta_{\text{inst}} = +0.296$, matching the +0.30 component) and 15/15 deactivation suppression. The 8-cell WT pool is therefore corroborated, not a small-sample artefact (verification card, 2026-09-21).

Grammar statement. Across all four channels drugs move steady-state occupancy/inactivation tables, not time-constant tables; the number and sign of separable action components is channel-specific. Operational form: a drug is a documented edit to named tables; “add one measured term” is consistently preferred over “re-fit a table”.

S5. Host-model integration and CiPA drug scoring (Stage B; ORd assembly)

Substitution registry (declared wording). I_{Kr} and I_{Ks} α -ised (tables of S1.1/S1.4 inserted into the O’Hara–Rudy human ventricular model¹⁴); I_{Na} registered failed arm, published ORd Markov

retained (basis: S1.2f); I_{CaL} published formulation retained ($Ca_v1.2$ not assembled, S1.3 scope).
Under no wording is this a four-channel assembly.

Host-level checks J1–J6 (all pass; definitions and measured values).

check	content	measured	band
J1 steady state	last-10-beat range	APD90 0.005 ms	below 0.5 ms
J2 morphology	APD90 / APA / RMP / qNet	251.206 ms (Δ 0.36%) / 128.51 mV / -87.99 mV / 0.056	APD90 $\pm 2\%$; APA $\in$ [124.4, 130]; RMP $\in$ [-95 , -85]; qNet $\in$ [0.05, 0.12]
J3a I_{Kr} -only swap	retrospective agreement	trace 1.1×10^{-5}	$\leq 1\%$
J3b I_{Ks} -only swap	four J1+J2 items	APD90 255.77 / APA 127.94 / RMP -88.00 / qNet 0.0717	all in band
J3c N-arm registration	expected-failure signature	APA saturated ≈ 40 mV; Δ APA = 3.1×10^{-5} mV under $G \times 16$	pre-registered expected failure (APA below 90 and Δ APA below 5 mV)
J4 upstroke	$dV/dt_{\max}$	240.7 vs reference 236.6 V/s (ratio 1.017)	$\in [50, 500]$ V/s
J5 rate dependence	APD90 monotonicity and capture	monotonic shortening in both arms; 1:1 capture throughout; max difference 2.5 ms	monotone + capture
J6 current magnitudes	peak-current ratios vs reference	I_{Kr} 2.06, I_{Ks} 1.52; sanity I_{Na} 0.997, I_{CaL} 0.979, I_{NaL} 1.009, I_{to} 1.002, I_{K1} 1.004	all $\in [0.2, 5]$

The I_{Kr} peak change by factor 2.06 during the action potential is a direct consequence of the data-extracted time structure of the repolarising current and is flagged as the substantive physiological difference from the Markov form; the largest sanity-current deviation is I_{CaL} at 2.1%. qNet on the composite 0.998 (unchanged from official baseline).

Stage B three-arm drug scoring (24 drugs; pre-registration revised to v6.1; dynamic-binding criterion^{2,3}).

arm	model	V1 ρ	V2 AUC
B1	official Markov 9-state + static Hill	-0.523	0.833
B2s	α -model + static binding	-0.506	0.833
B2	α -model + dynamic binding	-0.547 ($p = 0.0057$)	0.857

Incremental verdict (pre-registered section 6): B2dyn vs B1, $\rho -0.547 \leq -0.523$ and $AUC 0.857 \geq 0.833 \rightarrow$ “ **α non-inferior to official Markov**” holds (dynamic-binding criterion). B2s sits between the two: replacing the model is essentially equivalent; replacing static with dynamic binding is the only real gain. V1 line ≤ -0.60 not passed by any arm.

Robustness (sealed). $\tau_{act} \times \{0.3, 0.5, 1, 2\}$ spanning the full B6 uncertainty band (every arm all 24 drugs, per-arm independent G_α calibration): inter-arm V1 range $0.016 \leq 0.10$, V2 0.857–0.881 all pass, incremental verdict $\checkmark$ in all four arms: the B6 uncertainty does not enter the Stage B conclusion. $Q_{10} \in \{2.0, 3.0\}$ (6-drug stratified subset): zero per-drug rank flips. IC₅₀ official newCiPA convention (6-drug subset): $\rho -0.837 \rightarrow -0.717$, direction unchanged, magnitude slightly reduced; full-panel scores use the card-3 self-extracted (ka3) convention.

Ceiling localisation. All three arms stall at V1 $\rho \approx -0.51$ – $-0.55 \rightarrow$ the $1 \times C_{max}$ static-protocol convention is the bottleneck, not the model (independently re-establishing the original motivation of ref. 3 for moving to $25 \times C_{max}$). Under the APD90 metric all arms reach $\rho +0.55$ – $+0.63$ and AUC 0.86–0.88, uniformly better than the qNet metric; the official APD defect case (ranolazine) is reproduced synchronously by all three arms, not a model artefact.

Mechanism note. Static Hill at $1 \times C_{max}$ systematically overestimates block depth of slow-binding drugs (dofetilide dynamic 0.992 vs static 0.764); the dynamic arm faithfully reflects

binding-kinetics limitation, information content unique to the card-3 k_{on} library that no static arm can express.

Registrations (not hidden). metoprolol (low-risk; qNet 0.93–0.96 $\times$; suspected non-hERG-channel IC₅₀ table value) is the largest single-drug drag on V1; after its exclusion all three arms pass. clarithromycin is the only k_{on} defaulted to the library median. The Q_{10} bridge repairs τ tables but not steady-state tables. Anchor cell single point 16713003. dofetilide 500 beats $\approx$ 2.7 binding time constants (finite-beat effect on record). The first τ_{act} -arm run mis-executed a 6-drug subset due to a script condition bug; re-run of all 24 drugs after the v6.1 fix is on record (aborted case archived).

Earlier single-channel stage (historical context). A trapped-binding single-channel fixed-waveform module reached AUC = 0.810 (high vs low) but $\rho = 0.475$ (V1 not passed): the ceiling of any single-channel fixed-waveform indicator was measured and located before Stage B; the ORd host + multi-channel route is the only rational upgrade path, which is what Stage B executes.

S6. Data defects, negative arms and sensitivity ledger

hERG data-side register D1–D11 (summary). D1 over-subtraction leakage (060/016, inactivation/h chain); D2 σ contamination (047); D3 measured-target missing levels (110/047); D4 AP spike (014); D5 $h_{\text{ss}}(+50)$ negative values (016/060); D6 -40 mV y_{ss} artefact (excluded); D7 activation-block data insufficiency (all nine cells; τ_{act} not sealable, elevated to a registration band); D8 strong noise correlation (resolved by envelope-gate switch); D9 double subtraction possibly suppressing measured repolarisation peaks; D10 early read-file gaps (repaired); D11 activation-kinetics protocol recording failure (007/047; effective pool 7/9). Data-side closure: 060/016 baseline shift above $3 \times \text{MAD}$ established; 007/047/118/110 marginal outliers registered; 014 failure established model-side; raw-data re-subtraction (dofetilide-subtraction parameter review for 060/016/007/047) deferred to the next stage.

$Na_v1.5$ negative arms. $N\alpha$ -3 (activation-foot portability): verdict 1: the foot spread (s_{ref} CV 0.184) is real cell-to-cell biological variability, not measurement noise; verdicts 3/4: negative evidence under clamp-collapse contamination (Lei artefact model⁹), with the crossing-point subdivision $|\Delta V| \leq 2.1$ mV; whole-cell -40 mV activation foot is not portable. $N\alpha$ -4: $\tau_h(-40)$ and $P_{\text{o,peak}}$ are distributions (S1.2f); the N-arm is permanently closed. Data gaps (registered): recovery branch absent; slow inactivation unresolved; true m_{∞} requires full clamp-dynamic

modelling; $\tau_m \geq +10$ mV beyond amplifier bandwidth; temperature single point 35 °C (25 °C side only a 314 single-cell coarse Q_{10} anchor 1.4–1.8).

Ca_v1.2 gaps (registered as data requirements). (1) Full-voltage activation tables (single step voltage in dataset); (2) recovery $\tau_{\text{rec}}(V)$; (3) per-cell τ_f carriage (needs ≥ 100 ms pulses, Ca-3b suspended); (4) Q_{10} of τ_{fast} (not judgeable under a 40 ms window + $R^2 \geq 0.9$ gate; a window-length physical limit, not a falsification); (5) slow inactivation / use dependence (protocol does not cover); (6) cross-batch dispersion of f_{inact} (2026-09-21): characterization-batch anchors 0.73/0.44 (CV ≤ 0.14) versus drug-screen control segments 0.56/0.26 (CV 0.26/0.61, $n = 77/20$); batch-anchored use only; component-level contrasts unaffected (S1.3a cross-batch check). Temperature always as covariate. CHO overexpression ($\alpha + \beta_2 + \alpha_2\delta_1$); CaM overexpression/knockout perturbations absent; CDI mechanism chain (CaM–IQ) not in the model; only its macroscopic increment is sealed.

I_{Ks} gaps. τ_{deact} full table missing except the -40 mV anchored magnitude (S1.4d); $22 \rightarrow 37$ °C Q_{10} bridge (literature $Q_{10} \approx 2-3$ used as sensitivity arm); E43C/V324A constructs excluded (contamination risk).

Slow-memory boundary (all channels). The hERG slow-memory analysis (S3) bounds what memoryless table models can express; equivalent analyses were not possible for the other channels from available protocols and are registered as open.

Sensitivity ledger (sealed items affecting conclusions). hERG: B6 τ_{act} band, sealed out of Stage B (range 0.016); Q_{10}/E_{rev} sensitivity, pass, bridge-independent; anchor-cell single point, registered. Nav: Q_{10} coarse anchor, registered, not used in scoring. CaV: registered exclusion of cell 0016 (clamping suspect; peak-latency 38 ms independent corroboration), verdicts unchanged with and without. I_{Ks} : instantaneous-component boundary cell, registered exclusion; Q_{10} bridge, sensitivity arm only.

S7. Per-cell parameter master table and exclusion registry

Master table. Every per-cell measurement feeding the population verdicts of S2 is deposited as a single long-format table (per-cell master table, four channels, 2026-09-21; 18,710 rows: hERG 18,353, all from the six Lei automated-patch batches of the five-temperature panel; Na_v 1.5 323; I_{Ks} 24; Ca_v 1.2 10). Columns: channel, dataset, group, temperature, cell_id, parameter, voltage_mV, value, unit, ok, note. Nineteen parameter types are carried (E_{rev} , h_{ss} , m_{ss} ,

tau_rec, tau_h, tau_act, tau_inact, tau_deact_slow, tau_app, tau_decay, tau_slow_37C, E_chord, V_half_act, V_half_inact, k_act, s_ref, late_pct, Po_peak, Q10_tau_slow). The table is the single source for every population median/CV quoted in S2 and for Extended Data Fig. 8. Rows failing a pre-registered rule carry ok = false with the rule named in the note column; they are excluded from statistics but never deleted.

Pharmacology-arm table. The pharmacology-arm cells used for the robustness checks of S1.3a/S1.4d are deposited as a companion long-format table with the same schema (pharmacology-arm table, 2026-09-21; 361 rows): I_{Ks} drug arms (mefloquine 15 and DIDS 26 cells $\times V_{1/2}/k$; HMR-1556 subtraction 6 cells $\times V_{1/2}/k$), $Ca_v1.2$ (characterization-batch pre-drug f_{inact} : Ca^{2+} 6, Ba^{2+} 4; drug-screening batch 97 cells $\times$ pre-drug/drug f_{inact} pairs (one of the 98 records carries neither value, registered); grouped by drug $\times$ carrier $\times$ protocol variant), $Na_v1.5$ (63 valid cell $\times$ concentration conditions $\times$ fractional block of step current, five drugs). Drug-naïve and drug-treated measurements are carried as separate parameters (f_{inact} versus f_{inact_drug} ; V_{half_act} in the master table versus $V_{half_act_drug}$ in the arm table), and the arm table feeds Extended Data Fig. 8e,f,h,i. The sealed master table (18,710 rows) is unchanged; the arm table is an additive deposit.

Exclusion registry. All exclusions are tabulated in a five-category registry (90 entries, deposited as markdown and CSV): **A, data quality (73 entries):** e.g., staircase ramp not crossing zero so E_{rev} cannot be located (7 of 670 wells: C18, M19, F13, P17, B05, P24, N05); holding-segment noise gate (fit amplitude below 4σ) rejecting a recovery fit at a given voltage; per-voltage h_ss ok = false under small-signal/isochronal distortion; 4 of 336 I_{Ks} ABF files unreadable (float format) and 193 $\rightarrow$ 163 duplicate-export deduplication; sweep-level QC gates in the $Ca_v1.2$ Ba^{2+}/Ca^{2+} dataset. **B, protocol limitation (9):** the -80 mV holding-potential step is isochronally degenerate by construction in every Lei batch (statistic refused by rule, batch-wide); 4 s activation pulses too short for I_{Ks} (fits pinned at the 2.5 s upper bound, all excluded at $\geq +30$ mV); the $37^\circ C$ -100 mV step below the n threshold. **C, method boundary (5):** e.g., isochronal-approximation bias (+10–30%) voiding the synthetic-recovery statistic at $-100/-60/-20$ mV; 2% crossing not locatable for three $Na_v1.5$ foot-slope cells; one I_{Ks} boundary cell at the exclusion line. **D, forward-judgement failure (2):** the two recorded forward failures (Beattie cell 16704007 sine/AP arm, known problem cell; one of three $Na_v1.5$ C2 full-trace cells, mechanism documented). **E, registered real physics (1):** the $Na_v1.5$ single-channel dispersion at -40 mV (CV 0.77/0.60) judged genuine modal-gating fluctuation, not failure. The registry exists to make

one property explicit: exclusions are rule-driven, named and countable: no cell, sweep or voltage step leaves the analysis without a written reason.

S8. Third-party literature anchor layer (T4)

Independent published values were transcribed as external anchors for the temperature layer (post-hoc, registration-grade, no judgement lines; transcriptions deposited, third-party literature layer T4, 2026-09-21).

- **Vandenberg et al. 2006** (*Am. J. Physiol. Cell Physiol.* 291, C165–175; CHO cells; transcribed verbatim from the tabulation in Li et al. 2016, Fig. 3D): recovery $\tau_{\text{rec}}(-120\text{mV})$ 3.8 ms at 24 °C and 1.1 ms at 37 °C. The 24→37 °C ratio 3.45 matches the present 25→37 °C ratio 3.49 (5.31 → 1.52 ms), recomputed Q_{10} 2.60 versus the present sealed Q_{10} 2.84; deactivation (−120 mV) 24.7 → 12.4 ms (Q_{10} 1.7); inactivation (+40 mV) 3.2 → 0.87 ms (Q_{10} 2.72).
- **Zhou et al. 1998** (*Biophys. J.* 74, 230–241; HEK293, 35 °C; digitised from the re-plot in Li et al. 2016, Fig. 4, reading precision ± 0.15 ms): $\tau_{\text{rec}} -100 \text{ mV} \approx 0.6 \text{ ms}$ rising to −20 mV $\approx 2.5 \text{ ms}$ (present Lei 37 °C: 1.87 → 3.50 ms; ratios 1.5–3.1, same voltage-direction); $\tau_{\text{inact}}(+40\text{mV}) \approx 2.3 \text{ ms}$.
- **Di Veroli et al. 2013** (*Am. J. Physiol. Heart Circ. Physiol.* 304, H104–117; CHO, IonWorks, 20 °C): $\tau_{\text{rec}}(-100\text{mV}) \approx 1.9 \text{ ms}$; against the present 25 °C value 6.54 ms the ratio 3.4 falls outside the factor-3 band: registered, not reconciled (inter-laboratory absolute- τ dispersion $\geq 2\times$ is documented in the field, including above $2\times$ between Di Veroli and Vandenberg at the same voltage per Li et al. 2016).
- **Oliveira-Mendes et al. 2023** (*Clin. Transl. Med.* 13, e1266; HEK293, 384-well automated patch, 22/27/32/37 °C): action-potential-clamp repolarisation power maps across temperatures with a single time factor ≈ 2 , an effective AP-level $Q_{10} \approx 2$ averaged across gating processes, consistent in magnitude and direction with the present layer.

Full transcription-source entry (used for the Vandenberg and Zhou transcriptions above): Li, Z., Dutta, S., Sheng, J., Tran, P. N., Wu, W. & Colatsky, T., A temperature-dependent in silico model of the human ether-à-go-go-related (hERG) gene channel, *J. Pharmacol. Toxicol. Methods* **81**, 233–239 (2016), doi:10.1016/j.vascn.2016.05.005 (main-text ref. 24).

Convention notes: inactivation Q_{10} values are not cross-comparable (Vandenberg/Zhou triple-pulse fast inactivation, $\tau \approx 1\text{--}3$ ms, versus the present 1 s big-step bi-exponential fast component, 43.7–90 ms) and are registered as literature values only; deactivation has no voltage overlap (Vandenberg -120 mV; present staircase $-60/-40$ mV); the literature layer is post-hoc and carries no judgement lines; sealed verdicts anchor exclusively on the pre-registered references.

S9. CiPA-panel coverage survey (I_{K1} and I_{to})

The CiPA channel panel includes two further currents, I_{K1} ($K_{ir}2.1$) and I_{to} ($K_v4.3$). A structured search for public datasets carrying multi-protocol raw traces (reconnaissance card, 2026-09-21) found: for $K_{ir}2.1$, no public raw-trace dataset exists: the CiPA $K_{ir}2.1$ methods study (Sanson et al. 2019, *Assay Drug Dev. Technol.* **17**, 89–99; PMC6479253) deposits no recordings, and no other source meets the standard (same-cell multi-protocol raw traces, $n \geq 10$ cells, publicly downloadable). For $K_v4.3$, exactly one public raw-trace dataset exists (Kovacheva et al., *eLife* 2025, main-text ref. 16; Dryad doi:10.5061/dryad.76hdr7t6z; 2.10 GB of whole-cell voltage-clamp traces from substantia-nigra dopamine neurons at 37 °C, A-type current activation and inactivation protocols, 17 vehicle and 15 6-OHDA cells), with no second independent source. Three consequences are registered. First, $K_{ir}2.1$ is excluded from the present scope for the documented data-availability reason alone; it is in any case biophysically ill-matched to a time-constant pipeline (inward rectification arises from near-instantaneous block by intracellular Mg^{2+} /polyamines; the extractable content would be steady-state tables, per-cell G and $E_{rev}(K_{out}^+)$). Second, for $K_v4.3$ a registration-grade probe of the single existing dataset has now been completed (S10): the pipeline reproduces every anchor of the source study and registers one candidate discovery. Third, sealed claims for $K_v4.3$, and cross-laboratory corroboration of the kind achieved for hERG, await a second public dataset.

S10. $K_v4.3$ (I_{to}) registration-grade probe

Grade declaration. This arm was run on 2026-09-21 as a feasibility and registration-grade probe. It was not pre-registered, and no quantity in this section is sealed. The probe does not enter the four-channel sealed record; it is reported as a portability test and as a registered candidate discovery.

Dataset. Kovacheva et al. 2025 (main-text ref. 16; Dryad doi:10.5061/dryad.76hdr7t6z): whole-cell voltage clamp of A-type currents in identified substantia-nigra dopamine neurons at 37 °C;

availability protocol (conditioning -120 – -30 mV, test -20 mV), activation-foot protocol (-60 – -15 mV), HCN protocol (-80 – -100 – -120 mV); 17 vehicle and 15 6-OHDA-lesion cells.

Data-defect registry. 18 of 28 activation files carry a corrupted repeat series (currents of order 10^7 nA); repaired by a rule fixed before any group comparison (same-voltage repeats with max/min ratio above 5: keep the smaller-magnitude sweep). After repair, all peak currents fall in the physical 2–11 nA range. 3 of 13 lesion-group inactivation files have fewer than five conditioning points and were not fitted. 2–3 of 15 lesion-group HCN files lack the -100 – -120 mV traces. A first-pass fitting pitfall is on record: currents must be converted to nA before fitting, otherwise the Levenberg–Marquardt search stalls at the initial point (17 false convergences, repaired and registered).

Anchor reproduction (all six pass).

quantity	this probe	source study	verdict
$K_v4.3$ peak current –30 mV, vehicle	3.95 ± 0.37 nA (n = 17)	3.8 ± 0.4 nA	match
$K_v4.3$ peak current –30 mV, 6-OHDA	1.95 ± 0.26 nA (n = 11)	1.7 ± 0.3 nA	match
amplitude down-regulation	-51% ($p = 2 \times 10^{-4}$)	$\approx -50\%$ ($p < 10^{-4}$)	match
activation foot slope, group shift	$0.109 \rightarrow 0.078$ mV $^{-1}$ (-28% , $p = 2 \times 10^{-5}$)	slope change reported	direction match
availability group shift	$V_{1/2}$, $-61.8 \rightarrow -61.0$ mV ($\Delta 1.3\%$, $p = 0.35$)	no gating change beyond activation slope	match
HCN amplitude –120 mV	0.44 vs 0.40 nA ($p = 0.78$)	no group difference ($p = 0.98$)	match

Time-constant inventory (-20 mV test potential). Activation t_{10-90} : 1.00 ms (vehicle, n = 17) versus 1.02 ms (lesion, n = 11), invariant ($p = 0.80$). Exponential activation τ : 1.67 ms (CV 1.17, n = 12) versus 1.10 ms (CV 0.40, n = 8), registered ($p = 0.057$). Inactivation τ of the subtraction-

isolated $K_v4.3$ component: 40.6 ms (CV 0.22, $n = 11$) versus 100.4 ms (CV 0.26, $n = 4$), +148% ($p = 0.001$; interquartile ranges 31.5–44.4 versus 80.7–118.3 ms, non-overlapping). HCN τ_{act} : 666 versus 827 ms at -100 mV ($p = 0.22$); 294 versus 525 ms at -120 mV (nominal $p = 0.03$, registered open).

Candidate discovery registration. The post-lesion inactivation slowing (+148%) is corroborated model-independently (t_{50} : 34.3 $\rightarrow$ 120.3 ms, +251%, $p = 7 \times 10^{-6}$; bi-exponential fast component 25.3 $\rightarrow$ 52.0 ms). A series-resistance or clamp-quality explanation is rejected on two grounds: the within-group amplitude- τ correlation is not significant in the vehicle group ($\rho = -0.41$, $p = 0.212$, $n = 11$ over a six-fold amplitude range), and amplitude-matched cells differ 2.4- to 3-fold in τ across groups (lesion 2.87 nA $\rightarrow$ 123 ms versus vehicle 3.42/3.53/3.59 nA $\rightarrow$ 52/54/41 ms); the pooled correlation ($\rho = -0.57$, $p = 0.026$) is a Simpson effect of the group difference. A composition-dilution explanation is likewise rejected (the slowing sits in the $K_v4.3$ -attributed component itself, not in contaminating currents), and the direction is inconsistent with a raised $K_v4.2$ share ($K_v4.2$ -mediated currents inactivate faster). The finding conflicts with the source study's statement that biophysical properties beyond the activation slope are unchanged. Three resolutions remain open: (i) a genuine novel finding (the source study did not perform within-protocol subtraction); (ii) small-sample chance (post-QC lesion $n = 4$); (iii) an unregistered batch difference. Registered as a candidate discovery; independent replication requires new data. Literature context: inactivation τ is a documented functional control variable in this cell class (Haddjeri-Hopkins et al., eNeuro 2021: wild-type IA inactivation τ median 30.9 ms, $n = 83$, the same order as the vehicle 40.6 ms here; inactivation kinetics, not conductance, set rebound delay and pacemaker frequency), and inactivation τ is a documented modulation target (KChIP co-expression shifts $K_v4.2$ inactivation τ from 20 to 49 ms; KChIP4a suppresses $K_v4.3$ inactivation).

Relation to the main thesis. Fifth independent reproduction of the pattern “steady-state tables constant under condition; amplitude and slope rewritten”: availability midpoint unmoved (Δ 1.3%), activation slope rewritten (-28%), amplitude rewritten (-51%), HCN tables unmoved. Structurally homologous to the hERG drug grammar (amplitude-type edits), the $Ca_v1.2$ two-pool bidirectional edits and the I_{Ks} batch shift.

S11. Time-constant provenance and Stage-B usage

Every time constant quoted in this work, with its source, verdict grade, and whether the Stage-B CiPA scoring used that exact value. The usage answer is uniform: Stage B used the sealed tables below with no re-fitting; quantities not sealed entered Stage B only as pre-registered sensitivity arms, and the sensitivity sweep shows the conclusion does not depend on them (S5, inter-arm V1 range 0.016).

time constant	value(s) used	source	extraction	grade	in model	α	in assembly	ORd	in Stage B CiPA
hERG deactivation staircase $\tau_f / \tau_m / \tau_{late}$	S1.1a (0.191–24.05 s, –70 – –40 mV)	Beattie nine cells	bi-exponential staircase fits	sealed (CV 0.13–0.19)	yes (m-gate chain)	(m-	yes		yes (same table)
hERG repolarisation τ_r / τ_d	S1.1b (3.04–6.5 ms / 30.3–85.8 ms, –120 – –90 mV)	Beattie nine cells	recovery and tail fits	sealed	yes (τ_h / τ_m anchors)	($\tau_h /$	yes		yes (same table)
hERG engine τ_m anchors, $V \geq -40$ mV	S1.1f (9.8–0.29 s)	Beattie nine cells	slow-component medians	registered	yes		yes		yes, with $\tau_{act} \times \{0.3, 0.5, 1, 2\}$ sensitivity arm
hERG τ_{act} (+40 mV)	band 131–228 ms	Beattie nine cells	envelope fits (d- τ degenerate)	registrati on band (B6)	yes, as band	as	yes, band	as	sensitivity arm only; sealed out

time	value(s)					in	α	in	ORd	in	Stage
constant	used	source	extraction	grade		model		assembly		B CiPA	
											of the conclusio n
hERG populatio n $\tau_{\text{rec}}(V)$, five temperatu res	Q_{10} = 2.84 layer; 1.52 ms at 37 °C, −120 mV	Lei five- temperatu re panel	per-well DoE fits	sealed (Q_{10}); populatio n layer	no (validatio n only)	no		no		no	
$Na_v1.5$ $\tau_h(V)$	S1.2a (1.639– 0.270 ms, −30–+40 mV)	Lei Nav HEK, 35 °C	mono- exponenti al fits	sealed (mid- band CV $\leq$ 0.26; −30 mV CV 0.029)	yes			no (N- arm closed; ORd Markov retained)		no	
$Na_v1.5$ $\tau_m(V)$	S1.2c (0.075– 0.0216 ms)	same	fits in command -voltage coordinat es	registered , restricted	limited			no		no	
$Na_v1.5$ $\tau_h(-40\text{mV})$	median 1.03 ms, CV 0.772, n = 69	Tarasov cell- attached tables	source- study extraction , re- judged	distribute d	no (arm closed)			no		no	
$Ca_v1.2$ τ_f / τ_{slow}	6–12 ms / 50.0 ms	Ren FDA $Ca_v1.2$	bi- exponenti	compone nt-sealed	yes (inactivat			no (not assemble		no	

time	value(s)	source	extraction	grade	in	α	in	ORd	in	Stage
constant	used				model		assembly		B	CiPA
(+17 mV)	(Ca ²⁺), 41.6 ms (Ba ²⁺)	dataset	al inactivati on fits		ion block)		d)			
I_{Ks}	S1.4a	author	source-	sealed	yes		yes		yes	(same
$\tau_{act}(V)$	(22-point table, peak 8.91 s at -10 mV)	ground truth, Fedida 2024 data pack Zenodo 10421153 (digitised version verified $\leq 2.2\%$, K α -4)	verified, cross- paper anchored	(K α -2)					yes	(same table)
I_{Ks} delay $d(V)$	S1.4b (1.35– 0.42 s, author truth)	author ground truth, Zenodo 10421153 ; physical identity is τ_2 , the F2 concerted step (K α - 5)	source- verified	upgraded post-seal (K α -4)	yes		yes		yes	
I_{Ks} $\tau_{deact}(-40$	2.0 s (anchored magnitud	Chan 2023 dataset	in- window decay,	registered (apparent 0.40 s	yes, anchored magnitud	as + sensitivit	yes: 2.0 s + sensitivit		yes, same 2.0 s conventio	

time	value(s)				in	α	in	ORd	in	Stage
constant	used	source	extraction	grade	model		assembly		B CiPA	
	e band 2– 3 s)		arms A/B	rejected)	e		y arm (or per-cell free)	n	with sensitivit y arm	
$K_v4.3$	1.00 ms /	Kovache	probe	registrati	no		no		no	
τ_{act}	/ 40.6 ms	va 2025	extraction	on (not						
τ_{inact}	(vehicle); 100.4 ms (lesion)	dataset	(S10)	sealed)						

Where a value is described as registered, the model carries it with its registration wording and never as a sealed constant; Stage-B usage of registered quantities is always paired with a sensitivity arm.

SI Master Table. Five-channel parameter summary (population median $\pm$ spread; verdicts)

quantity	hERG	$Na_v1.5$	$Ca_v1.2$	I_{Ks}	$K_v4.3$ (registration grade)
current form	$G m h (V - E_{rev})$	$G m^3 h (V - E_{rev})$	$G m h P(V)$ (inactivation block)	$G a (V - E_K)$	not assembled (probe only)
E_{rev}	−88.33 mV (sealed)	+72–+75 mV (registered, weak)	+45.2 $\pm$ 2.5 mV (Ba ²⁺ , sealed)	−85 mV (registered)	not extracted
kinetic portability	τ_{deact} CV 0.13–0.19 (sealed)	τ_h mid-band CV $\leq$ 0.26; −30 mV CV 0.029 (sealed)	τ_f 6–12 ms; τ_{slow} 50.0/41.6 ms (group)	$\tau_{act}(V)$ cross- paper anchored; τ_{deact} magnitude 2–	activation t_{10-90} invariant across conditions

					$K_V4.3$ (registration grade)	
quantity	hERG		$Na_v1.5$	$Ca_v1.2$	I_{Ks}	
					3 s anchored	(1.00/1.02 ms, p = 0.80)
kinetic failure	τ	none	$\tau_h(-40)$ median 1.03 ms, CV 0.772, n = 69 (distributed)	: per-cell (needs long pulses)	τ_f τ_{deact} apparent 0.40 s rejected; single-value unification failed (CV 0.313)	τ_{inact} rewritten by condition (40.6 $\rightarrow$ 100.4 ms, +148%, p = 0.001; candidate discovery)
steady-state slope	h_{ss}	12-level measured table	$k_h = 4.79$ mV (sealed)	n/a	k = 22.6 mV (methodology footnote)	activation foot slope rewritten -28 % by condition
steady-state midpoint	per-cell (h_{pop} fallback)		$V_{1/2,h}$ -66.1 + $\Delta_{cell}, \pm 4$ mV (per-cell)	= n/a	$V_{1/2} = 25.05$ mV (pool, zero deviation vs source anchor)	availability $V_{1/2}$ invariant (-61.8 $\rightarrow$ -61.0 mV, p = 0.35)
activation midpoint	m_{ss}	re-split anchors	$V_{1/2,m}$ portable artefact)	not (Rs)	not assembled (in a_{ss})	not sealed (foot-only protocol)
per-cell parameters	free	G only	G + $\Delta V_{1/2,h}$	G only (inactivation block)	G only	n/a (not assembled)
forward record	sine 7/9; 8/9; CiPA	AP (	full trace 3/3 ≤ 3.4 %	component- level (no full	activation 7/8; inst	source-study anchors 6/6

quantity	hERG	$Na_v1.5$	$Ca_v1.2$	I_{Ks}	$K_v4.3$ (registration grade)
	65/68; whitening 28/33	RMS)	model)	0.062 vs 0.10	reproduced
drug action	amplitude- type on h_{ss} ($ \kappa^* - 1 =$ 0.020); pure block rejected (ϵ_x 0.088 > 0.030)	dual component $\Delta f = +0.12$; external 7/7 in $\pm 50\%$	amplitude- type (κ^* -0.01); pools +0.168 / -0.088 ; pure block rejected (ϵ_x 0.223 > 0.139 ; $p =$ 7.2×10^{-16})	multi-table (a_{ss} shift, inst +0.30, deact suppression); DIDS confounded	condition arm is a lesion, not a drug; amplitude/slo pe rewritten, other tables unmoved
host-model status	α -ised (ORd)	Markov retained (N- arm closed)	not assembled (data gap)	α -ised (ORd; τ_{deact} 2.0 s + sensitivity)	not assembled

S12. Evidence-strength register

Added 2026-09-24. This register classifies every headline quantitative claim of the main text by the type of evidence beneath it, states the known soft spot of each claim, and points to the judgement card, verification card or SI section where the defence lives. Its purpose is to make the attack surface of this paper explicit before a referee has to compute it. Card names cited in the Basis column are the verbatim archived filenames listed in the submission-package validation records index (05_validation_records_index.md); two cited artefacts, the Stage-B recompute receipt (audit_receipt_StageB_recompute_recheck_2026-09-21.json) and the $K_v4.3$ probe verification card (verification_card_Kv43_probe_2026-09-21.md, v2), are real archived files not yet listed in that index and are registered here for its next revision. Entry prefixes: H = hERG, N = $Na_v1.5$, C = $Ca_v1.2$, K = I_{Ks} , V = $K_v4.3$, B = host integration (Stage B), P = methodology and pipeline.

Tier definitions. Tier 1 (recompute-proof): exact mathematics verified numerically, or end-to-end recomputation from raw or entry-level data; survives hostile recomputation with the same inputs. Tier 2 (bounded): solid within the stated conventions; the soft spot (small sample, single dataset, digitised source, temperature bridge, registration band) is registered next to the claim. Tier 3 (calibrated wording): the direction of the claim is established, but the numerical magnitude is convention-dependent; the wording is bounded accordingly, or flagged in S12.3 where a bound is still pending.

S12.1 Register of headline claims

hERG (I_{Kr}).

ID	Claim (location)	Tier	Basis	Soft spots, registered
H1	Zero-fit forward sinusoid (95% Wilson CI 45–94%), AP-clamp 8/9 (57–98%), CiPA traces 65/68 across three laboratories (88–99%), residual whiteness 28/33 (Fig. 2c, d; SI S2)	hERG 2	Sealed judgement and assembly cards 2026-09-13_alpha_model_two_protocol_forward_closures_verdict_pending_audit.md, 2026-09-14_alpha_model_formal_assembly_model_card.md, preregistration_alpha_model_CiPA_cross_lab_verification_card_2026-09-14.md; SI S1.1, S2	Nine-cell base from a single study (the only manual-patch dataset with all six protocols in the same cells); Wilson intervals wide; exact binomial intervals quoted and corroboration placed outside the construction set (H2); both forward failures attributed on record (data-side 047/060, model-

ID	Claim (location)	Tier	Basis	Soft spots, registered
				side 014; S6)
H2	Population-level corroboration on the independent 211-cell automated-patch panel: E_{rev} CV 0.024 (n = 209); negative-limb h_{ss} 1.000/0.955; deactivation ladder 0.74/3.03 s preserved; AP- clamp magnitude and frequency ordering reproduced; per- cycle criterion 45.8% registered (Results; SI S2; Extended Data Fig. 7)	2	verdict_card_L ei211_alpha_po pulation_verdi ct_2026-09- 21.md under frozen preregistered_ verdict_card_L ei211_alpha_po pulation_2026- 09-21.md (four pre-run amendments archived); SI S2	Bridge crosses temperature (25 vs 37 °C), platform (automated vs manual patch) and protocol family; the claim is signature-level reproduction, not identity; the A1 per-cycle criterion is registered, not sealed; three stated panel limitations (sub- steady-state activation pulses; isochronal bias band; re-leak correction step)
H3	Refutation of $h = 1$ at negative voltages; twelve- level measured availability table carried ($h_{ss}(-70 \text{ mV}) =$	2	SI S1.1c; nine- cell extraction record 2026-09- 13_alpha_model _campaign_clos ure_verdict_pe nding_audit.md	Per-level n = 3– 8; –80 mV data- limited; +50/+60 mV via the R3 endpoint policy; several levels registered rather

ID	Claim (location)	Tier	Basis	Soft spots, registered
	0.425) (Fig. 2a; SI S1.1c)			than sealed (verdict column of Table S1.1c)
H4	hERG pharmacology is amplitude-type: pure block rejected 30/30 ($\varepsilon_x = 0.088 >$ 0.030); $ \kappa^* - 1 $ $= 0.020$; temporal warp absorbs $\approx 15\%$ (Fig. 2e; SI S4)	2	SI S4 library run (136/136 datasets judgeable, 517 cell-units); 2026-09- 14_alpha_model _StageB_three_ way_comparison _verdict_card. md; drug pre- registration cards 5/6 (preregistrati on_alpha_model _drug_card5_sh ape_invariance _verdict_2026- 09-14.md, preregistratio n_alpha_model_ drug_card6_sha pe_deformation _decomposition _2026-09- 14.md)	κ^* rises slightly with concentration (ρ $= 0.39$), a sub- threshold temporal component registered; concentration- time confound under incremental dosing registered; conclusion unchanged at relaxed threshold 0.08
H5	Identifiability analysis of the 13-parameter Markov	1	Symbolic verification of the two exact degeneracies	The analysis object is our own interim model62 formulation

ID	Claim (location)	Tier	Basis	Soft spots, registered
	formulation: $\chi = 7.4 \times 10^{12}$, six null directions, two exact degeneracies, 0/451 loop inversions (Results; Extended Data Fig. 2; SI S3)		plus automatic-differentiation Fisher spectrum; judge_model62_identifiability_2026-09-11.md; model_card_model62_external_math_form_and_parameters_2026-09-11.md; SI S3.0, S3	standing for the globally fitted class; class-representativeness is argued, not proved; model62 known defects documented in S3.0
H6	Slow-memory analysis: history-dependent currents differ by factors 17–112 (9/9 cells); continuous memory spectrum 4.8 s to beyond 2,000 s (Results; SI S3)	1	Direct measurement on all nine cells; SI S3; 2026-09-13_alpha_model_campaign_closure_verdict_pending_audit.md	The continuum is explicitly not claimed; the discrete-component tables capture only the dominant modes; equivalent analyses were impossible for the other channels from available protocols (S6); the bound applies to any memoryless table model, ours

ID	Claim (location)	Tier	Basis	Soft registered spots, included
H7	Five-temperature layer: $\tau_{\text{rec}} Q_{10} = 2.84$ ($R^2 = 0.991$) sealed; 37 °C cross-platform absolute check ratio 0.50 inside [0.3, 3] sealed; endpoint $Q_{10} = 1.50/1.83$ sealed at the endpoints; $\tau_2(-40 \text{ mV}) Q_{10} = 7.6$ out of band, registered (Extended Data Fig. 6; SI S2)	2	verdict_card_L_ei_temperature_Q10_2026-09-21.md under preregistered_verdict_card_L_ei_temperature_Q10_2026-09-21.md; post-seal three-layer check verification_card_tau_rec_grid_quantization_continuum_refinement_recheck_2026-09-21.md (continuous refit 2.26/2.89; model-free clocks 2.1–3.8; Vandenberg anchor 2.60); SI S8 literature layer	Arrhenius linearity not established (grid-quantised plateaus, one non-monotone midpoint); the 37 °C –140 mV point is resolution-censored (55% of cells at the grid floor); the T4 literature layer is post-hoc and carries no judgement lines
H8	τ_{rec} extraction boundary: the 22-point logarithmic grid (23% step) under-resolves	2	verification_card_tau_rec_grid_quantization_continuum_refinement_recheck_2026-09-	Method boundary, registered: no per-cell claim relies on sub-grid precision; the

ID	Claim (location)	Tier	Basis	Soft spots, registered
	the fastest (1–2 ms) recovery values; the striped groups of Extended Data Fig. 8c are grid quantisation; the sealed Q_{10} is shown not to be inflated by the grid (SI S2; Extended Data Figs. 6, 8c)		21.md (1,340 correctly seeded continuous refits; the mis-seeded artefact $Q_{10} \approx 0.9$ identified, discarded and archived)	censored 37 °C –140 mV point is registered, not used

$Na_v1.5$ (I_{Na}).

ID	Claim (location)	Tier	Basis	Soft spots, registered
N1	$\tau_h(V)$ mid-band constant ($CV \leq 0.26$; –30 mV extrapolation $CV \leq 0.029$); full-trace forward 3/3 (RMS $\leq 3.4\%$ against the 8% line) (Fig. 3a; SI S1.2a, S2)	2	verdict_card_N a1_Nav15_inactivation_fast_component_constancy_2026-09-15.md; verdict_card_N a2_Nav15_whole_channel_validation_2026-09-15.md; control battery S1/S2/S2b/S3 all pass (self-	Three cells, one dataset, one temperature (35 °C); the –20 mV level is an activation-foot protocol boundary (registered; value used, constancy not counted)

ID	Claim (location)	Tier	Basis	Soft spots, registered
			consistency $R^2 = 1.000000$)	
N2	$\tau_h(-40 \text{ mV})$ single-point anchoring fails: a 69-patch distribution (median 1.03 ms; CV 0.772; range 0.31–6.64 ms; correlation with late-current fraction $\rho = 0.44$); the N-arm is closed and I_{Na} retains the ORd Markov form (Fig. 3b; SI S1.2f; Extended Data Fig. 3d)	1	Distribution statistics recomputed from the source study's published extraction tables; verdict_card_Na4_Nav15_single_channel_minus40_anchor_verdict_2026-09-16.md under preregistration_Na4_Nav15_single_channel_minus40_anchor_verdict_2026-09-16.md; mechanism corroborated by the source study itself (ref. 20; SI S1.2f)	Registered as an active adjudication (a clean negative result), not a defect; the spread is not removable by quality filtering; citation discipline: this level must not be cited as a single value; the sealed mid-band domain $-30 - +40 \text{ mV}$ is unaffected
N3	Activation-foot slope s_{ref} : sealed pool WT+BC2 (n = 12; median 0.267 mV^{-1} ; CV 0.184; Cochran	2	verdict_card_Na3_Nav15_activation_foot_portability_verdict_2026-09-16.md under preregistratio	Negative arms 3/4 under clamp-collapse contamination handled by the crossing-point

ID	Claim (location)	Tier	Basis	Soft spots, registered
	Q = 77.9 >> $\chi^2_{0.95}(11) = 19.7$, genuine biological dispersion); not portable across constructs ($\Delta\text{KPQ} -34.9\%$) or laboratories (Lei 0/3 within the band) (Extended Data Fig. 3c; SI S6)		n_Na3_Nav15_activation_footportability_verdict_2026-09-16.md	subdivision ($ \Delta V \leq 2.1$ mV); the whole-cell -40 mV activation foot is not portable
N4	m_∞ registered as not portable (series-resistance artefact; $V_{1/2,m}$ spread 11.8 mV); $E_{\text{rev}} \approx +72$ – $+75$ mV weakly identified (SI S1.2d, e)	2	SI S1.2d, e; independent artefact-model corroboration (refs 9, 15)	No reversal bracket; I–V fit with 2/3 cells at the upper bound; m_∞ used only in command-voltage coordinates (C1 self-consistent forward 3/3)
N5	$Na_v1.5$ drug action dual- component ($ \kappa^* $ = 0.20; use- dependence consistency $\Delta f =$ $+0.12$); external	2	verdict_card_Na_drug_Nav15_drug_shape_modulation_verdict_2026-09-15.md under preregistration_Na_drug_Nav1	The remaining external comparisons are 3-point- insufficient (verdict wording fixed)

ID	Claim (location)	Tier	Basis	Soft spots, registered
	benchmark panel 7/7 within a $\pm 50\%$ band (Fig. 4; SI S4)		5_drug_shape_m odulation_verd ict_2026-09-15.md	accordingly, not IC_{50} mismatches); 63 valid cell $\times$ concentration conditions

$Ca_v1.2 (I_{CaL})$.

ID	Claim (location)	Tier	Basis	Soft spots, registered
C1	CDI as an additive fast component: $w_{fast} = 0.289$ against the independent carrier-swap estimate $\Delta f = 0.293$ (1.4% agreement); τ_f 6–12 ms; τ_{slow} 50.0/41.6 ms (Fig. 3c; SI S1.3b)	2	verdict_card_C a3_CDI_structu re_verdict_202 6-09-15.md under preregistratio n_Ca3_CDI_stru cture_verdict_ 2026-09-15.md; Ba^{2+} negative control 0/4	3/6 cells separable; identifiability boundary $\tau_f \gtrsim 14$ ms inside a 25 ms fit window ($C \propto -3b$ suspended; adjudication needs ≥ 100 ms pulses); the cross-check is a same-batch cross-carrier contrast
C2	Absolute inactivated fractions $f_{inact}(+17 \text{ mV}, 40 \text{ ms}) = 0.73$ (Ca^{2+}) /	3	verification_c ard_drug_arm_r obustness_IKs_ and_CaV_2026-09-21.md; SI	Characterization- batch values sit at the upper quartile of the cross-batch

ID	Claim (location)	Tier	Basis	Soft spots, registered
	0.44 (Ba ²⁺): batch-anchored; the drug-screen pre-drug control segments give 0.558 (n = 77, CV 0.26) / 0.258 (n = 20, CV 0.61) (Fig. 3c; SI S1.3a cross-batch check; S6 item 6)		S1.3a protocol lock (“+17 mV, 40 ms window, this external solution”)	distribution; cross-batch dispersion roughly doubles (CV 0.26/0.61 vs ≤ 0.14); Verapamil-RT variant (0.87) a registered batch confound; all component-level conclusions are same-batch or same-cell contrasts and are unaffected; wording ledger S12.3
C3	Ca _v 1.2 drug 2 action: pure block rejected ($\varepsilon_x = 0.223 >$ 0.139 ; paired Wilcoxon p = 7.2×10^{-16}); amplitude-type on average ($\kappa^* =$ −0.01) with bidirectional inactivation pools (+0.168 /		verdict_card_C a5_CaV12_drug_ shape_modulati on_verdict_202 6-09-15.md under preregistratio n_Ca5_CaV12_dr ug_shape_modul ation_verdict_ 2026-09-15.md; carrier cross- validation	Nominal concentrations unavailable (no dose- deformation relation); methadone facilitatory cells mixed into the main pool (registered); vp- Ca-RT external comparison

ID	Claim (location)	Tier	Basis	Soft spots, registered
	−0.088) (Fig. 4; SI S4)		reproduces the source-paper signs (SI S4)	abstained (insufficient sample)
C4	Temperature policy: $Q_{10}(G)$ is not a cross-cell constant; temperature carried as an explicit covariate with no uniform Q_{10} correction (SI S1.3c)	2	verdict_card_C a4_ramp_chord_ conductance_te mperature_law_ 2026-09-15.md; preregistratio n_Ca1_CaV12_in activation_tem perature_law_c arrier_verdict _2026-09- 15.md; preregistratio n_Ca4_ramp_IV_ temperature_la w_2026-09- 15.md	Channel-specific finding (contrast with the hERG constant- Q_{10} bridge registered); most per-cell regressions R^2 below 0.5; group medians reported descriptively
C5	Full $Ca_v1.2$ – channel model not assembled: activation- coverage protocols absent from the available dataset; the inactivation block is component- sealed (SI S1.3		SI S1.3, S6; model_card_CaV 12_alpha_model _math_form_and _parameters_20 26-09-15.md	Status declaration, not a result: the gap is registered as a data requirement, not an omission

ID	Claim (location)	Tier	Basis	Soft registered	spots,
	sealed scope; S6 gap 1)				
<i>I</i> _{KS} (KCNQ1+KCNE1).					
ID	Claim (location)	Tier	Basis	Soft registered	spots,
K1	$\tau_{\text{act}}(V)$ bell-shaped table (peak 8.91 s at -10 mV), author ground truth (Fedida 2024 data pack, Zenodo 10421153); earlier digitised version verified point-by-point $\leq 2.2\%$ ($K \alpha -4$); cross-paper check ratio 1.29 passes (Fig. 3d; SI S1.4a)	1	verdict_card_Ka2_IKs_cross_paper_tau_act_comparison_2026-09-15.md under preregistration_Ka2_IKs_cross_paper_tau_act_comparison_2026-09-15.md; verdict_card_Ka4_Zenodo10421153_truth_comparison_2026-09-26.md	22 °C single temperature; our 4 s protocol values are lower bounds; $K \alpha -2$ verdict: simulations take this table preferentially	
K2	Two-component form with pool constant $\beta = 0.30$; activation forward 7/8 ($R^2 \geq 0.80$); instantaneous-	2	verdict_card_Ka1_IKs_activation_deactivation_constancy_verdict_2026-09-15.md; verdict_card_Ka3_IKs_forward	WT pool 8 cells (corroboration in K4); delay table upgraded to author ground truth 2026-09-26 ($K \alpha -4$; sealed	

ID	Claim (location)	Tier	Basis	Soft spots, registered
	component error 0.062 against the 0.10 line; $V_{1/2}$ zero-deviation anchor against the source value (25.05 vs 25.4 mV) (Fig. 3d; SI S1.4, S2; Extended Data Fig. 5)		_validation_20 26-09-15.md under their pre- registrations	runs used the digitised version, shift ≤ 0.19 s, direction-neutral, registered); mechanistic identity of $d =$ F2 concerted step ($K \alpha^{-5}$); gold- standard pipeline test passed ($K \alpha^{-6}$; SI S1.4e); isochronal normalisation systematically $\approx$ 16 % shallower than the peak-tail convention (methodological footnote, registered)
K3	$\tau_{\text{deact}}(-40 \text{ mV})$: 2 apparent single- sweep value 0.40 s rejected as a recording- window artefact (arm A 0/8); absolute magnitude 2–3 s anchored; per-		verdict_card_K a1_IKs_activat ion_deactivati on_constancy_v erdict_2026- 09-15.md; verdict_card_K a3_IKs_forward _validation_20 26-09-15.md	Citation discipline fixed ("apparent value rejected; absolute magnitude anchored; per- cell spread real"); the full τ_{deact} table is missing except

ID	Claim (location)	Tier	Basis	Soft spots, registered
	cell spread CV 0.313 genuine (SI S1.4d; Extended Data Fig. 5d)		(arms A/B)	the −40 mV anchor; ORd assembly uses 2.0 s plus a sensitivity arm
K4	WT 8-cell pool 2 corroborated by the 15-cell mefloquine arm: same-pipeline G–V fits R^2 median 0.994; instantaneous elevation 15/15 sign-consistent (median +0.296 against the +0.30 grammar prediction); deactivation suppression 15/15 (SI S4)		verification_c ard_drug_arm_r obustness_IKs_ and_CaV_2026- 09-21.md; pharmacology- arm table (SI S7)	The arm cells are drug-treated extractions: the relation is same- pipeline robustness plus per-cell grammar fulfilment, not a larger sample of the same quantity; DIDS arm pool- confounded in the source data and reported as such
K5	I_{Ks} drug 2 grammar multi- table: batch- dependent a_{ss} shift, instantaneous component +0.30,		verdict_card_K a_drug_IKs_dru g_table_decomp osition_verdic t_2026-09- 15.md under preregistratio n_Ka_drug_IKs_ drug_table_dec	Batch-dependent shift component; the cross-batch WT reference in the K α -drug JSON (vh_med 32.12 / k_med 19.05) must not

ID	Claim (location)	Tier	Basis	Soft registered spots,
	deactivation slowing (Fig. 4; SI S4)		omposition_verdict_2026-09-15.md	be mixed with the pool-internal convention (25.05 / 22.6), registered

$K_v4.3$ (I_{to} ; registration-grade probe).

ID	Claim (location)	Tier	Basis	Soft registered spots,
V1	All six source-study anchors reproduced: peak currents 3.95/1.95 nA vs published 3.8/1.7 nA; $\approx$ 50% amplitude down-regulation; activation slope shift -28% ; availability midpoint and HCN current invariant (Extended Data Fig. 9; SI S10)	2	verification_card_Kv43_probe_2026-09-21.md (v2, superseding v1 after spike-artefact repair; correction trail on record); SI S10 anchor table; feasibility_card_Kir21_Kv43_dataset_availability_2026-09-21.md	Single dataset with no second public source (S9); 18/28 activation files carried a corrupted repeat series, repaired by a rule fixed before any group comparison; probe not pre-registered
V2	Candidate discovery: inactivation time constant of the	3	verification_card_Kv43_probe_2026-09-21.md (v2); SI S10	Not pre-registered; post-lesion $n = 4$; conflicts with the

ID	Claim (location)	Tier	Basis	Soft spots, registered
	subtraction-isolated $K_v4.3$ component slows from 40.6 ms (n = 11) to 100.4 ms (n = 4) after lesion (+148%; p = 0.001; interquartile ranges non-overlapping); series-resistance and composition-dilution explanations tested and rejected (Extended Data Fig. 9; SI S10)		candidate-discovery registration, including the model-independent corroboration (t_{50} +251%)	source study's no-gating-change statement; three resolutions remain open (novel finding / small-sample chance / unregistered batch difference); registered as a candidate discovery awaiting new data; wording ledger S12.3
V3	Grade difference: – the $K_v4.3$ arm is a registration-grade probe; nothing in SI S10 is sealed; it does not enter the four-channel sealed record (SI S10 grade declaration; Fig. 3a legend)		SI S10 grade declaration; feasibility_card_Kir21_Kv43_dataset_availability_2026-09-21.md	Status declaration: sealed $K_v4.3$ claims and cross-laboratory corroboration of the hERG kind await a second public dataset

Host-model integration (Stage B).

ID	Claim (location)	Tier	Basis	Soft spots, registered
B1	ORd host 1 integration passes all six host-level checks J1–J6: APD90 difference 0.36%; retrospective trace agreement 1.1×10^{-5} ; I_{Kr} peak ratio 2.06 flagged as the substantive difference; every other current within 2.1% (Fig. 5a, b; SI S5)	1	verdict_card_0 Rd_three_chann el_alpha_assem bly_2026-09-16.md; verdict_card_alpha_model_StageB_B3_dual_alpha_host_recheck_2026-09-16.md; SI S5 check table	Quantitative identity of the repolarising currents explicitly not claimed; every disagreement localised to a named measured table; N-arm retained as published Markov (basis S1.2f)
B2	Three-arm CiPA 1 scoring under the dynamic-binding criterion: $\rho = -0.523$ / -0.547 / -0.506 , AUC 0.833–0.857; the α arm is non-inferior to the official arm (Fig. 5c, d; SI S5)	1	Independent end-to-end recompute receipt audit_receipt_StageB_recompute_recheck_2026-09-21.json: $\rho = -0.523177$ / -0.547022 / -0.506346 against the sealed -0.5232 /	24-drug panel; pre-registration revised to v6.1 on record; the first τ_{act} -arm run mis-executed (script condition bug) and the corrected re-run is archived; clarithromycin k_{on} defaulted to

ID	Claim (location)	Tier	Basis	Soft spots, registered
			−0.5470 / the library −0.5063 , digit- median exact at card (registered) precision; SI S5	
B3	The V1 ceiling 2 near −0.55 is an attribute of the 1 × Cmax static protocol and scoring data, shared by all three arms; metoprolol carries a data- side question, after whose exclusion all arms pass (Fig. 5d; SI S5)		SI S5 ceiling localisation and registrations; Stage B cards of B1/B2	The ceiling statement binds the scoring convention, not any model; metoprolol's suspected non- hERG IC₅₀ table value is a registration, not an established fact; under the APD90 metric all arms reach ρ +0.55−+0.63 (context, same section)
B4	The τ_{act} 1 registration band (B6) is sealed out of the Stage-B conclusion: sensitivity arms ×{0.3, 0.5, 1, 2} spanning the full band give inter-		2026-09- 14_alpha_model _B6_open_case_ three_candidat e_verdict_summ ary.md; recompute receipt as in B2 (τ_{act} sensitivity range 0.016363	The band itself remains registered, not sealed, awaiting +50/+60 mV activation data; H2 (cross-cycle accumulation) is the surviving

ID	Claim (location)	Tier	Basis	Soft spots, registered
	arm V1 range 0.016 (Fig. 5e; SI S1.1, S5, S11)		against sealed 0.016); SI S11 usage table	main explanation with a quantitative prediction card on record; residual gap 2.1– 2.6× registered
B5	The Q_{10} bridge 2 repairs τ tables but not steady- state tables (SI S5 registrations; SI S11)		SI S5 registrations; verdict_card_L ei_temperature _Q10_2026-09- 21.md; sensitivity arm $Q_{10} \in \{2.0, 3.0\}$ with zero per- drug rank flips (6-drug stratified subset)	Scope registration: steady-state temperature dependence is unbridged; bridge values never enter scoring without a paired sensitivity arm

Methodology and pipeline.

ID	Claim (location)	Tier	Basis	Soft spots, registered
P1	Extract–judge– assemble discipline: pre- registered verdicts frozen before any prediction; no	1 (procedure)	SI S2 verdict classes and scoring; SI S7 exclusion registry; failed_cell_re gister_four_ch annels_2026-	The measurement- noise CV estimation is protocol-family specific (SI S2 conventions); the

ID	Claim (location)	Tier	Basis	Soft spots, registered
	global fit at any stage; exclusions rule-driven and tabulated (90-entry registry, five categories) (Methods; SI S2, S7)		09-21.md	registry quantifies discipline and does not by itself validate any number
P2	Deposited per-cell master table (18,710 rows) and pharmacology-arm table (361 rows) as the single source of every population statistic (SI S7; Extended Data Fig. 8)	1 (deposit)	SI S7; Extended Data Fig. 8 panels regenerate from the two tables	hERG rows dominate (18,353 of 18,710, all from the Lei automated-patch batches); ok = false rows are excluded by named rules and never deleted
P3	model62 reference formulation: our own interim construction with documented defects, used only as the Fisher-analysis object and as an independent-	2	model_card_model62_external_math_form_and_parameters_2026-09-11.md; SI S3.0 calibration record	Fails nine-cell cross-validation (calibration cell only); since $R^2 = 0.95404$ misses its 0.955 line (architecture-level shortfall); the transitional name “model62-

ID	Claim (location)	Tier	Basis	Soft spots, registered
	convention reference (SI S3.0)			chain” corrected in v05
P4	CiPA-panel coverage survey: no public raw-trace dataset exists for $K_{ir}2.1$; exactly one for $K_v4.3$; consequences registered (SI S9)	2	feasibility_card_Kir21_Kv43_dataset_availability_2026-09-21.md; SI S9	Absence-of-dataset claims are search-date stamped (2026-09-21) and could be invalidated by new deposits
P5	Production notes – (not evidence items): code repository published at github.com/lihua_nlz/alpha-ion-channel-models (a permanent DOI via Zenodo archiving can be minted at submission); Acknowledgements written (data-provider credits); Author contributions		Main-text v05 endnote TODO list; external-audit form-layer register (external_audit_package_v04_2026-09-21.md, section 6)	Form-layer items with no content risk; listed here so the register is complete

ID	Claim (location)	Tier	Basis	Soft registered	spots,
	deferred to the journal-submission version; reference-numbering repairs pending (refs 4/14 merge, 9/11 split, ref. 19 full citation, first-citation renumbering) (main-text v05 endnote; Methods)				

S12.2 What the tiers add up to

Thirty-six headline entries: eight Tier 1, twenty-three Tier 2, two Tier 3, and three status or production declarations (C5, V3, P5). No claim requires retraction. The two Tier 3 entries (C2, batch-anchored absolute inactivation fractions; V2, the $K_v4.3$ candidate discovery) carry wording that must stay at the calibrated level; the formulations are collected in S12.3. Every entry's basis resolves to a named archived card, a deposited receipt, or a section of this SI; no entry rests on unwritten evidence, and no main-text claim was found without a resolvable basis during the compilation of this register.

S12.3 Wording ledger (calibrated formulations)

Entry	Main-text wording	Status
C2	“the steady-state inactivated fraction at +17 mV in the characterization batch is 0.73	Applied 2026-09-24: main text now carries the batch anchor verbatim; the protocol lock is

Entry	Main-text wording	Status
	(Ca ²⁺) versus 0.44 (Ba ²⁺) (batch-anchored; cross-batch dispersion registered, SI S1.3a)”	carried in SI S1.3a
V2	“we register it as a candidate discovery awaiting new data rather than a sealed result”	Current wording already calibrated
N2	“We report this as a quantitative property of the available Na_v 1.5 data, not as a modelling failure”	Current wording already calibrated
B3	“all arms share a performance ceiling near -0.55 under the 1 $\times C_{max}$ static protocol, which is an attribute of the protocol and scoring data rather than of any model”	Current wording already calibrated
H7	“sealed at the endpoints, Arrhenius linearity not established because of grid- quantised plateaus and one non-monotone midpoint” (Extended Data Fig. 6 legend)	Current wording already calibrated