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General Theory of Gating (GTG): from Hodgkin–Huxley to a calculus of composable gates for voltage-gated ion channels

Technical report

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Abstract

The General Theory of Gating (GTG) defines a unified mathematical framework for voltage-gated ion-channel modelling through bounded gate dynamics and explicit interactions among reusable activation–inactivation modules. It extends the classical Hodgkin–Huxley (HH) formalism through nonlinear occupancy and coupled kinetic routes while retaining independent HH gating as an exact limiting case. Building on the generalised HH (gHH) model for human ligand-gated receptors, GTG expresses activation, inactivation, recovery, delayed onset, persistent current and tail current within a common compositional calculus. A dedicated modelling language and compiler generate model equations, derivatives, fitting workflows and simulation tools. Representative human cardiac sodium and native microglial potassium-current models illustrate the construction. The resulting theory and computational infrastructure support comparative channel biophysics, larger physiological models and potential translational applications in disease modelling, variant interpretation, safety pharmacology and drug discovery.

1. Scientific purpose and contribution

Voltage-clamp experiments provide a command voltage and a macroscopic current, while the internal gating processes remain hidden. Channel-specific HH variants and Markov schemes often require different architectures and bespoke implementations. GTG addresses this fragmentation by defining reusable gates, modules, directed interactions and current readouts within one mathematical framework. The central questions are which effective gating mechanisms explain observed current behaviour and which constructions can be reused across channel families.

The published gHH framework describes human P2X and AMPA receptor currents using coupled activation and inactivation gates and structured current formulations [1]. GTG extends this foundation from a fixed receptor-model architecture to a general calculus of composable gating objects [2, 3]. The theory defines the model class; channel-specific models instantiate it; and the modelling language, compiler and integrated tools provide its computational realisation.

1.1 Gates, modules and interaction graphs

A GTG module consists of a pair of gates: an activation gate m and an inactivation/availability gate h. For example, $M_0 = (m_0, h_0)$. Each module has its own internal coupling, and modules can interact with other modules or with a non-module gate such as a delay gate d. Larger architectures are assembled by extending the same construction, rather than introducing an unrelated theory for each channel [2].

A directed interaction represents modulation of the receiving gate's forward and backward kinetic routes, not a microscopic state transition or chemical conversion. Reciprocal coupling comprises two directed interactions. Modules represent effective kinetic components; the interaction graph, local rates and current readout specify how those components generate the measured current [2].

2. Mathematical construction

2.1 Nonlinear occupancy and modulation

The univariate and bivariate homotopy functions and the nonlinear occupancy kernel are defined as follows [2].

$$F(x;\kappa,n) = (1-\kappa) + \kappa x^n \tag{1}$$

$$G(x,y;\ \kappa,n_1,n_2) = (1-\kappa) + \kappa x^{n_1} y^{n_2} \tag{2}$$

$$f(x;c) = x + cx(1-x) \tag{3}$$

The variables x and y, or their complements, lie in [0, 1]. The coupling coefficient κ lies in [0, 1], the occupancy-curvature parameter c lies in [−1, 1], and the modulation exponents are positive integers. F describes single-gate modulation, while G lets a source module act through both of its gates. The occupancy kernel reduces to the classical linear availability factor when c is zero.

2.2 A coupled activation–inactivation module

For a module $M = (m,h)$, the paired directional modulation factors are:

$$A_{\alpha_{hm}} = F\left(h;\kappa_{hm},n_{\alpha_{hm}}\right) \tag{4}$$

$$A_{\beta_{hm}} = F\left(1-h;\kappa_{hm},n_{\beta_{hm}}\right) \tag{5}$$

$$A_{\alpha_{mh}} = F\left(1-m;\kappa_{mh},n_{\alpha_{mh}}\right) \tag{6}$$

$$A_{\beta_{mh}} = F\left(m;\kappa_{mh},n_{\beta_{mh}}\right) \tag{7}$$

The corresponding activation and inactivation dynamics are:

$$\frac{dm}{dt} = \alpha_m(V)A_{\alpha_{hm}}f(1-m;\ c_m) - \beta_m(V)A_{\beta_{hm}}f(m;\ c_m) \tag{8}$$

$$\frac{dh}{dt} = \alpha_h(V)A_{\alpha_{mh}}f(1-h;c_h) - \beta_h(V)A_{\beta_{mh}}f(h;\ c_h) \tag{9}$$

The local α and β rates depend on the clamped voltage V. In the h equation, α_h governs recovery and β_h governs inactivation. The activation gate and its complement modulate these opposing routes. Reciprocal directions can share κ or use separate coupling coefficients and exponents [2].

2.3 Module composition and the HH limit

Inter-module interactions supply paired factors through G. Multiple incoming modulators are combined by the declared operator $\odot$, using a product or an arithmetic average; an absent set of modulators contributes one. Setting all coupling coefficients and occupancy-curvature parameters to zero recovers independent classical HH gating [2].

2.4 Example current equation

The current equation maps the module dynamics to the observable current. An additive two-module readout is:

$$I = \left(g_{M_1}m_1^{n_1}h_1^{n_2} + g_{M_2}m_2^{n_3}h_2^{n_4}\right)(V - V_r) \tag{10}$$

Here g_{M_1} and g_{M_2} are the two module conductances, V_r is the reversal potential, and $n_1 - n_4$ are the current exponents. The two activation–inactivation products contribute additively and share the driving force. GTG also permits multiplicative and hybrid readouts within the same modelling grammar [1, 2].

3. Computational realisation and demonstrations

3.1 GTG tooling system and compiler

Figure 1 summarises the GTG tooling architecture. A `model.gtg` source file declares gates, modules, interactions, current expressions, rate laws, parameter bounds and sharing rules, together with experimental protocols and data mappings. The parser validates these declarations before the compiler constructs the interaction graph and generates the numerical model [3].

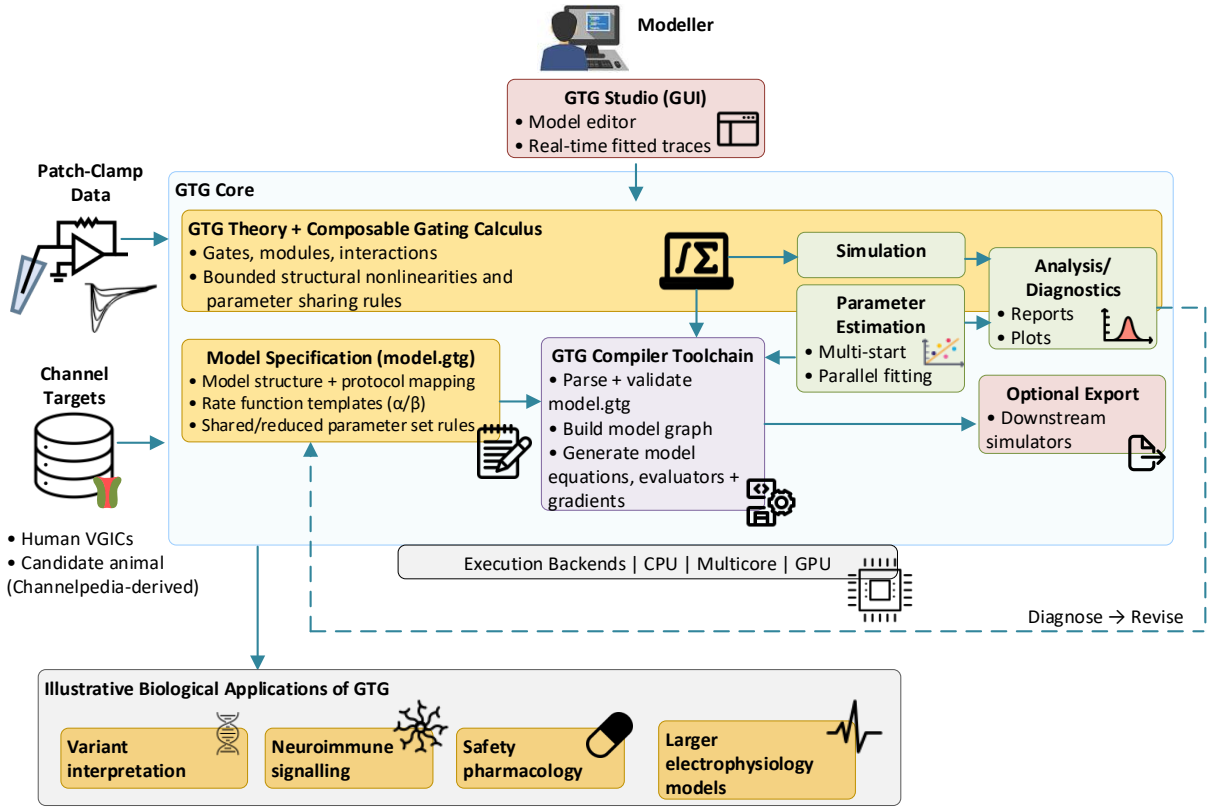


Figure 1. GTG tooling architecture. The compiler links model specifications to equations, numerical evaluators and derivatives. Fitting and diagnostic output support iterative model revision, while export connects fitted models to downstream simulations. GTG Studio and GPU acceleration are development targets [3].

The current implementation uses MATLAB for parsing and workflow orchestration, with generated C++ MEX functions for current evaluation, initial conditions and integration of the ordinary differential equations (ODEs) with exact parameter sensitivities. The native Levenberg–Marquardt backend provides bounded and geodesic policies, reusable numerical workspaces and persistent worker threads. The fitting workflow supports multi-start optimisation, shared parameters, restartable runs and live fit diagnostics [3].

Protocols can be defined as pulses or imported command waveforms. Recovery from inactivation can be specified for calibration or as a post-fit virtual experiment. The compiler produces equation reports, fitted-current and branch-current plots, and standalone simulators. Learned positive monotone rate tables can be retained or distilled into compact analytic expressions. The GTG-VMS extension composes fitted channels into membrane-voltage simulations [3].

GTG Studio is being developed as a native integrated environment for editing model specifications, building models, running fits and visualising results. It brings the same scientific source model into an interactive workflow for experimental and computational users [3].

3.2 Human cardiac sodium-current example

Human cardiac $Na_v1.5$ recordings contain several coordinated current regimes, including delayed onset, rapid activation and inactivation, persistent current and repolarisation tails. A GTG model combines a delay gate with four activation–inactivation modules to represent these features within one coupled construction. Figure 2 shows representative experimental–model comparisons at two test voltages [2].

$$\mathrm{d} \rightleftarrows \mathrm{M}_0 \rightleftarrows \mathrm{M}_1 \rightleftarrows \mathrm{M}_2 \rightleftarrows \mathrm{M}_3$$

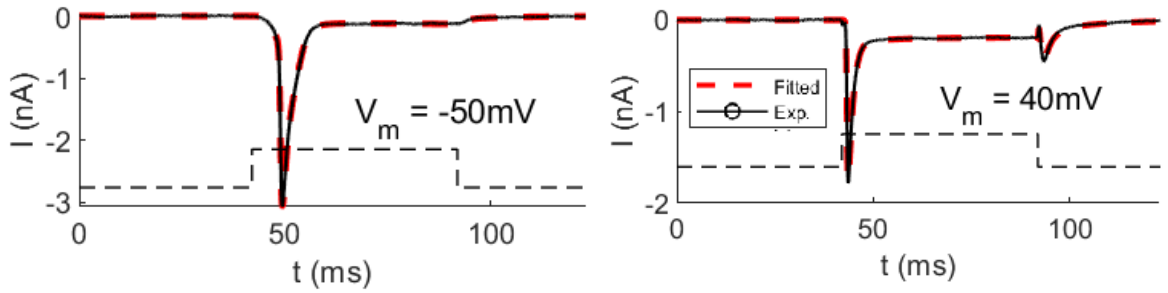


Figure 2. Human cardiac $Na_v1.5$ currents at −50 mV (left) and +40 mV (right). Red dashed curves show the fitted currents; black curves and symbols show the experimental recordings. The coupled model captures the early, peak, persistent and tail features [2].

The current readout combines separate early and peak-shaping terms with a grouped late contribution from the remaining modules. Branch-current analysis links these readout terms to different temporal features while retaining the interactions between the underlying gates. The same model specification determines the fitted equations and their computational evaluation [2, 3].

3.3 Native human microglial potassium-current example

Native human microglial K_v recordings display a multi-feature current profile rather than a single simple transient. Four interacting GTG modules reproduce the early and intermediate features, the broader late component and the persistent current. Figure 3 compares a representative fitted trace and the current–voltage relationship with experimental data [2].

$$\mathrm{M}_0 \rightleftarrows \mathrm{M}_1 \rightleftarrows \mathrm{M}_2 \rightleftarrows \mathrm{M}_3$$

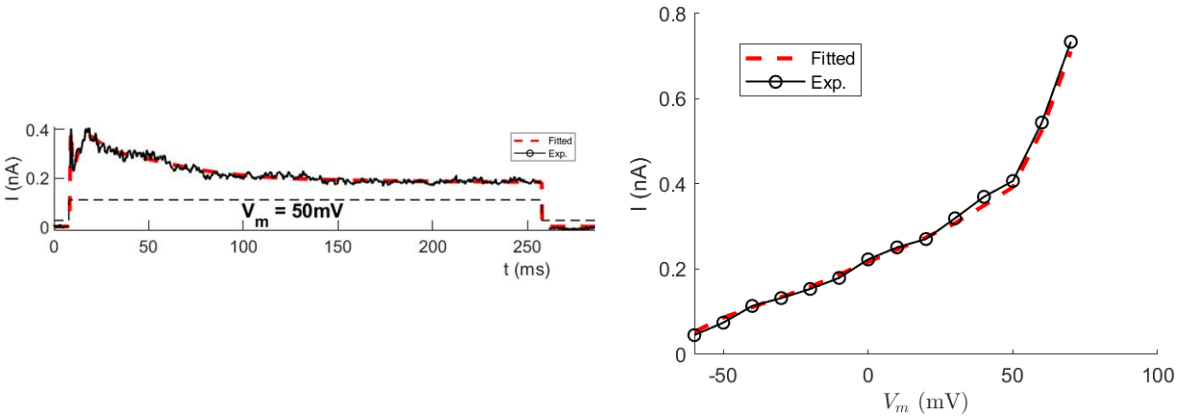


Figure 3. Native human microglial potassium-current modelling. Left: experimental and fitted current at +50 mV. Right: the corresponding current–voltage relationship. Four coupled activation–inactivation modules represent the multi-feature kinetics within the GTG grammar [2].

The microglial and cardiac examples use the same bounded gate variables, module construction and coupling rules. Their differences are expressed through the arrangement of modules, local

rates, interaction parameters and current readout. This provides a common description of distinct current phenotypes and a route from channel-level modelling to cellular electrophysiology [2].

4. Impacts for computational physiology and translation

GTG provides a common mathematical basis for comparing ion-channel dynamics across sodium, potassium and calcium channel families. Reusable modules and explicit kinetic interactions allow activation, inactivation, recovery, persistent and tail behaviours to be expressed using the same modelling principles. Differences between channels can then be studied through module arrangement, coupling, rate dependence and current readout rather than through incompatible model descriptions. This supports cumulative model development in channel biophysics and comparative electrophysiology [2].

For computational physiology, fitted GTG channels provide components for larger membrane, ionic-homeostasis and signalling models. In human microglia, potassium-current models can be integrated with purinergic receptor currents, calcium handling, pumps and exchangers to investigate how channel activity shapes membrane potential and neuroimmune signalling. The same compositional principle supports neuronal, cardiac and enteric-glial modelling, connecting channel kinetics to cellular responses relevant to brain, heart and gut physiology. GTG-VMS supplies a computational route for assembling fitted channel components into membrane-voltage simulations [3].

The translational potential lies in connecting altered current phenotypes to defined model components. Disease-associated variants and pharmacological perturbations can be compared through changes in local rates, inter-module coupling, conductance and current readout. Such analyses can generate testable hypotheses about channel dysfunction, guide targeted experiments and support human-relevant disease modelling. Compact, reusable channel models also provide a foundation for future ion-channel drug discovery, variant interpretation and safety-pharmacology workflows. These are intended applications of the framework rather than established clinical outcomes.

For experimental electrophysiologists, the tooling system links recordings to interpretable model structures, fitted currents, current decomposition and simulation. For computational researchers, generated equations, derivatives and portable simulators reduce repeated implementation work and facilitate model reuse. Planned open specifications, software, benchmark protocols and model libraries will support reproducible comparison and further development across laboratories. The resulting connection between theory, computation and electrophysiology is the central practical contribution of GTG [2, 3].

5. Research outputs and continuing development

The mathematical theory and the computational platform are being developed in two complementary manuscripts: the GTG theory paper [2] and the GTG Compiler and GTG Studio paper [3]. Continuing work extends the channel-model library, multi-protocol evaluation, the native software platform and the interactive environment. The objective is a reusable ecosystem in which the model specification, generated mathematics, fitting workflow and simulation outputs remain linked through a common scientific representation.

References

[1] Poshtkohi A, Gulbransen BD. Generalised Hodgkin–Huxley model captures human P2X and AMPA receptor currents. The Journal of Physiology. 2026;604:214–246. doi:10.1113/JP288880.

[2] Poshtkohi A, Dallas ML, Al-Owais M, Ozsoy N. General Theory of Gating (GTG): from Hodgkin–Huxley to a calculus of composable gates for voltage-gated ion channels. Manuscript in preparation, 2026.

[3] Poshtkohi A, Dallas ML, Al-Owais M. GTG Compiler and GTG Studio: an executable modelling language and native integrated development environment for ion-channel model discovery. Manuscript in preparation, 2026.