SUPPORTING INFORMATION S2

The uncoupled DA and its Markov Chain equivalent

The inaccuracy of the uncoupled form of the Diffusion Approximation algorithm to represent stochastic channels with multiple gating particles has been extensively studied numerically and analytically [1,2,3,4,5]. As shown analytically by [5], the uncoupled DA is accurately representing another type of MC modeling. To confirm this numerically that this is the case (i.e. the DA approximation works also in the uncoupled scenario) we compared the uncoupled particles DA algorithm with an uncoupled version of the MC modeling. This was to show that the uncoupled DA implementation behaves as independent, two-state MCs where the conductance is calculated over the fraction of active gating particles (see Figure S1).

Figure S2A shows results of the Rubinstein’s Node of Ranvier model testing for both coupled and uncoupled MCs and DA algorithms. See Figure 2B and 2D in the main text for a description of left and middle panels, respectively; and Figure 3 for the right panel. Figure S2B shows results of the spontaneous action potential firing observed in the HH model with the uncoupled and coupled versions of DA and MC modeling. Figure description is as in Figures 6A and 6D of the main text. These results confirm that the uncoupled DA perfectly matches the behavior of uncoupled MCs in both models under current clamp testing. As we explain in Supporting Information S3, this is also true for voltage clamp simulations (Figure S3D and S3F). Thus, given that the DA is appropriately implemented, it will always approximate very closely the behavior of exact Markov Chain modeling; what makes a difference is the coupling or uncoupling of gating particles.

We want to note that to simulate uncoupled MCs not only means to switch from N 5-state (K) or 8-state (Na) to 4N 2-state MCs. If the conductance is calculated as the fraction of channels that have all gating particles active, then this is a coupled particles scenario. However, this type of simulation requires keeping track of each gating particle and channeling individually [6], making impossible to apply the efficient channel number tracking algorithm employed here (see Methods and [7]). Our definition of uncoupled MCs implies that the conductance is calculated over the fraction of active particles (Figure S1), an approach that may seem wrong when in the context of MCs but that nevertheless is exactly what the uncoupled DA is representing.

Methods: Simulation of Uncoupled independent particles

N channels are simulated as 4N independent, 2-state particles:

\[ a_0 \xrightarrow{\alpha_a} a_1 \]

where \( \alpha_a \) is the transition probability from the 0 to the 1 state, and \( \beta_a \) the transition probability from the 1 to the 0 state. \( N_{Na} \) Sodium channels are simulated as \( 3N_{Na} \) \( m \) particles and \( N_{Na} \) \( h \) particles, and at each time step the sodium conductance is calculated as

\[ g_{Na} = \frac{g_{Na}}{3N_{Na}} \left( \frac{Nm}{3N_{Na}} \right)^3 \left( \frac{Nh}{N_{Na}} \right). \]  

(1)
where $Nm_1$ and $Nh_1$ are the number of $m$ and $h$ particles in the ‘1’ (active) state, respectively. $N_k$ potassium channels are simulated as $4N_k n$ particles and the potassium conductance is calculated as

$$g_k = g_k \left( \frac{Nh_1}{4N_k} \right)^4. \tag{2}$$

$Nn_1$ is the number of $n$ particles that are in the ‘1’ state.

**Diffusion Approximation**

The DA in the case of independent particles uses the variables $m$, $h$, and $n \in [0,1]$ to keep track of the fraction of $m$, $h$, and $n$ particles, respectively, that are in the ‘1’ state. It follows immediately that the fraction of particles in the ‘0’ state will be $1-m$, $1-h$, and $1-n$, respectively. Fox and Lu [8] showed that the time evolution of the variables is given by the SDE

$$\frac{da}{dt} = \alpha_a (1-a) - \beta_a a + \sigma_a(t) \xi(t) \tag{3}$$

where $a$ represents either $m$, $h$ or $n$. The stochastic term $\xi(t)$ is a Gaussian white noise with zero mean and unit variance that is scaled by $\sigma_a(t)$, being

$$\sigma_a(t) = \sqrt{\frac{\alpha_a (1-a) + \beta_a a}{N_a}} \tag{4}$$

where $N_a$ is the number of $a$ particles ($N_m=3N_{Na}$, $N_h=N_{Na}$ and $N_n=4N_k$). When the steady state approximation was used, the noise scaling factor was calculated as

$$\sigma_a(t) = \sqrt{\frac{2\alpha_a \beta_a}{N_a (\alpha_a + \beta_a)}} \tag{5}$$

The conductance of sodium and potassium are calculated using the classical Hodgkin & Huxley expressions

$$g_{Na} = g_{Na} m^3 h \quad \text{and} \quad g_k = g_k n^4.$$
References


**UNCOPLED INDEPENDENT ACTIVATION SUBUNITS**

Markov Chain modeling

$N$ channels = $4N$ independent
2-state subunits

Differential Equations

One ODE or SDE
(2 for sodium channels)

Conductance

Calculated on the basis of $n$,
the fraction of active subunits

$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

$$g_K = \bar{g}_K n^s$$

(for Markov chains, $n = \frac{N_a}{N}$)

**COUPLED INDEPENDENT ACTIVATION SUBUNITS**

Markov Chain modeling

$N$ channels = $N$ independent 5-state MCs (8-state for Na)

Differential Equations

One ODE or SDE per state

Conductance

Calculated on the basis of $n_a$, the
fraction of channels with all
subunits active

$$g_K = \bar{g}_K n_a$$

(for Markov chains, $n_a = \frac{N_n}{N}$)

**Figure S1**
Figure S2