Comparisons of wave dynamics in Hodgkin-Huxley and Markov-state formalisms for the sodium (Na) channel in some mathematical models for human cardiac tissue

Mahesh Kumar Mulimani,^{1,*} Alok Ranjan Nayak^{2,†} and Rahul Pandit^{1,‡}

¹Centre for Condensed Matter Theory, Department of Physics, Indian Institute of Science, Bangalore 560012, India

²International Institute of Information Technology (IIIT-Bhubaneswar), Gothapatna, Po: Malipada, Bhubaneswar 751003, India

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We compare and contrast the excitation properties of cardiac myocytes and cardiac tissue modeled by (a) a Hodgkin-Huxley-model (HHM) and (b) Markov-chain-model (MM) formalisms for the sodium (Na) ion channel. Specifically, we bring out the differences between HHM and MM formalisms, for both wild-type (WT) and mutant (MUT) models, for ion-channel kinetics, single-myocyte action potentials, and the spatiotemporal evolutions of spiral and scroll waves in different mathematical models of cardiac tissue. We show that the kinetic properties of Na ion channels are not the same for HHM and MM models; in particular, the range of values of the trans-membrane potential V_m , in which there is a significant window current, depends significantly on these models, so there are marked differences in the opening times of the Na ion channels, the maximal amplitude of the Na current, and the presence or absence of a late Na current. Furthermore, these changes lead to different excitation behaviors in cardiac tissue; specifically, two of the WT models show stable spiral waves, but the other one shows meandering and transiently breaking spiral waves. Our results are based on extensive direct numerical simulations of waves of electrical activation in these models, in two- and three-dimensional (2D and 3D) homogeneous simulation domains and also in domains with localized heterogeneities, either obstacles with randomly distributed inexcitable regions or mutant cells in a wild-type background. Our study brings out the sensitive dependence of spiral- and scroll-wave dynamics on these five models and the parameters that define them. We list desiderata for a good model for the Na wild-type ion channel; we use these desired properties to select one of the MM models that we study.

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I. INTRODUCTION

The development of an understanding of the dynamics of waves of electrical activation in cardiac tissue is a problem of central importance in research on life-threatening cardiac arrhythmias, because sudden cardiac death is responsible for roughly half of the deaths from cardiovascular disease, i.e., 15% of all deaths globally [1]. Approximately 80% of sudden cardiac deaths arise from ventricular arrhythmias [1]. Such arrhythmias are often associated with the formation of spiral or scroll waves of electrical activation; unbroken spirals or scrolls lead to ventricular tachycardia (VT), whereas broken waves, with spiral- or scroll-wave turbulence [2–7], are responsible for ventricular fibrillation (VF); VT and VF lead to the malfunctioning of the pumping mechanism of the heart, so, in the absence of medical intervention, VF leads to sudden cardiac death. It is very important, therefore, to study VT and VF by using all means possible, namely, *in vivo*, *in vitro*, and

in silico investigations, which play complementary roles. *In silico* investigations require mathematical models for cardiac cells (cardiomyocytes or, simply, myocytes) and for cardiac tissue.

The electrical behavior of cardiac myocytes can be studied by using the Hodgkin-Huxley model (HHM) [8], which considers the opening and closing of voltage-gated ion channels; the gates are described by deterministic, first-order, ordinary differential equations (ODEs); in an HHM each gating variable is independent of other gating variables. However, ion channels are proteins that can have many conformational states and, therefore, channels open and close stochastically; hence, discrete-state Markov models (MMs) have been developed to model ion channels; in some cases, these Markov models can be reduced to HHMs [9]. Clearly, these Markov models are more general than HHMs; in particular, the discrete states in an MM depend on each other; and MMs have more parameters than HHMs.

Markov-state models are especially useful in studies concerning ion-channel mutations such as those that lead to the LQT2 and LQT3 syndromes [10–13]. In particular, such studies have elucidated the effects of different mutations on the myocyte action potential (AP) [11] and the interaction between drugs and the discrete states in an MM [13–15].

Recently it has been shown that, at the level of a single cardiomyocyte, the dynamics of wild-type (WT) and mutant (MUT) ion channels can be modeled well by the HHM formalism, if it is obtained from the Markov-state model

*maheshk@iisc.ac.in;

†aloknayak@iiit-bh.ac.in;

‡rahul@iisc.ac.in; also at Jawaharlal Nehru Centre For Advanced Scientific Research, Jakkur, Bangalore, India

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(MM) [16]. In particular, HHM action potentials, their morphological properties, the action-potential-duration restitution (APDR), and the conduction-velocity restitution (CVR) are comparable to their MM counterparts [16]. The authors of [16] have considered both WT and MUT cases for Kr and Na channels in the MM and their HHM counterparts; their results are encouraging, insofar as they suggest that we can use simple, effective HHM models, whose parameters are obtained from comparisons with their complicated MM counterparts, to obtain the properties of action potentials and their dependence on mutations. A careful comparison of these MMs and the HHM for an ion channel, at the cellular level, brings out the differences in their action potentials and their morphologies. To compare the characteristic properties of excitation waves in these models, it behooves us to carry out studies of spiral-wave dynamics in homogeneous and heterogeneous tissue in two-dimensional (2D) simulation domains; we embark on such a study here. In particular, we focus on the dynamics of Na channels in the MM and HHM models, as the Na channel is important in controlling the upstroke velocity and the threshold for excitation at the cellular level, and the CV at the tissue level. Finally, we perform a parameter-sensitivity analysis for action-potential biomarkers like the action-potential-duration (APD), maximal value of V_m ($V_{\max}$), resting membrane potential (V_{rest}), and the conduction-velocity CV in all the WT models. We show that the cellular model parameters, which control the above biomarkers, show variations in the controlling pattern in all the three WT models. We list desirable properties for a good model for the Na wild-type ion channel; we use these properties to select one of the MM models that we study. The remaining part of this paper is organized as follows. Section II is devoted to methods and simulations. In Sec. III, we report our results for single-cell studies and tissue-level simulations in 2D square and 3D slab domains for WT models; we also present, for MUT models, single-cell and 2D-simulation results. We also report the parameter sensitivity analysis performed on all the five models. Furthermore, we list desiderata for selection of a good Na ion-channel Markov model out of many such Markov models. Section IV, Discussion and Conclusions, contains a discussion of the significance of our results. Some of the details of our study are given in Appendices; e.g., Appendix A details about the numerical implementation, and the protocols we use for our study; Appendix B details about convergence analysis and the accuracy; Appendix C details about spiral-wave dynamics in MM1 WT and MM2 WT models, with two different values of the diffusion constant D . We discuss in Appendix D the application of our spiral-wave control scheme in all the four Markov models we consider. We discuss in Appendix E the parameter-sensitivity analysis used in our study and, finally, in Appendix F, we compare the run times for simulations of TP06 and all the Markov models we consider here.

II. METHODS AND SIMULATIONS

A. Model

The parent single-cell action-potential model is the one used in the TP06 model Ref. [18]. Here, the Hodgkin-Huxley

formulation of the Na ion channel and, specifically, the gating-variable dynamics are formulated by using the experimentally determined, human, cardiac wild-type Na ion-channel dynamics of Ref. [41]. Our study focuses on the Na ion channel; therefore, we use one of the most sophisticated formulations for the Na ion channel, namely, the one used in the TP06 model. Even though the O'Hara-Rudy (ORd) model Ref. [36] is more recent than the TP06 model, many groups have suggested that the Na ion-channel formulation in ORd model should be replaced with that of the TP06 model Ref. [42]. Furthermore, that TP06 model has been studied extensively; and this model captures various properties of spiral-wave dynamics that are observed in cardiac tissue. The Na-channel mutations, which we consider, occur in the SCN5A gene of the Nav1.5 membrane ion-channel protein; these mutations are observed in cardiac myocytes; and they lead to the LQT3 syndrome [44–47]. The Markov model MM1 MUT considers the Y1795C mutation in the SCN5A gene; and the Markov model MM2 MUT considers the Δ KPQ mutation in the SCN5A gene. Both these mutations are responsible for delayed inactivation resulting in a small, sustained, late Na current in the repolarization regime [44,45]; this causes early after depolarizations (EADs), which are responsible for the premature-ventricular contractions (PVCs) that can lead to dangerous arrhythmias.

The electrical behavior of a single cardiac myocyte is governed by the following ordinary differential equation (ODE) for the transmembrane potential V_m :

$$\frac{dV_m}{dt} = -\frac{I_{\text{ion}}}{C_m}; \quad (1)$$

$$I_{\text{ion}} = \sum_{i=1}^{12} I_i; \quad (2)$$

here, I_{ion} is the sum of all the ionic currents, I_i is the current because of the i th ion channel, and C_m is the normalized, transmembrane capacitance. In the parent TP06 model, I_{ion} is the sum of the following 12 ionic currents (for details see Table III in Appendix A):

$$I_{\text{ion}} = I_{\text{Na}} + I_{\text{CaL}} + I_{\text{to}} + I_{\text{Ks}} + I_{\text{Kr}} + I_{\text{K1}} + I_{\text{NaCa}} + I_{\text{NaK}} + I_{\text{pCa}} + I_{\text{pK}} + I_{\text{bNa}} + I_{\text{bCa}}. \quad (3)$$

The spatiotemporal evolution of V_m , at the tissue level, is governed by the following nonlinear reaction-diffusion partial differential equation (PDE):

$$\frac{\partial V_m}{\partial t} = D \nabla^2 V - \frac{I_{\text{ion}}}{C_m}, \quad (4)$$

where D is the diffusion constant; for simplicity, we consider the case in which D is a scalar.

B. Hodgkin-Huxley model

The TP06 model uses the Hodgkin-Huxley formalism for the WT Na channel. The macroscopic current through this channel is governed by the three gating variables m , h , and j [18]; the first of these is an activation gate and the latter two

FIG. 1. Schematic diagrams for Markov Models for Wild-Type (WT) and Mutant (MUT) cases: (Top) MM1 WT and MM2 WT models; the MM1 WT model has 9 states, namely, the open state (**O**), the closed states (**C1**, **C2**, **C3**), and the inactivation states (**IF**, **IM1**, **IM2**, **IC2**, **IC3**); the MM2 WT model has 8 states, namely, the open state (**O**), the closed states (**C1**, **C2**, **C3**), and the inactivation states (**IF**, **IS**, **IC2**, **IC3**). The orange, double-headed arrows indicate transitions between such Markov states; transition rates for the rightward (leftward) transition are given above (below) these arrows, e.g., a_{111} (b_{111}) for the **IC3** $\rightarrow$ **IC2** (**IC2** $\rightarrow$ **IC3**) transition in MM1 WT. (Bottom) Schematic diagrams for the MM1 MUT and MM2 MUT models; the MM1 MUT model has the same number of states as the MM1 WT model, but the transition rates between the Markov states are different; the MM2 MUT model has 12 states: 8 of these are as in the MM2 WT model; in addition there are 4 bursting states, namely, **BO**, **BC1**, **BC2**, and **BC3**.

are inactivation gates; the gating dynamics and the Na current are given by

$$\frac{da_n}{dt} = \frac{a_\infty - a_n}{\tau_n} \quad [\text{here } a_n \text{ can be } m, h, \text{ or } j]; \quad (5)$$

$$I_{\text{Na}} = G_{\text{Na}} m^3 h j (V_m - E_{\text{Na}}). \quad (6)$$

G_{Na} is the maximal sodium-channel conductance, a_∞ is the steady-state value of a_n , τ_n the time constant of this gating variable, and E_{Na} is the sodium-channel Nernst potential.

C. Markov-state models

We consider four Markov-state models (MMs): two of these are for the wild-type (WT) and the other two for the mutant (MUT) Na channels. We use the Markov-state formalisms of [19] for the first WT and MUT Na channels; we refer to these as Markov-model-1 wild-type (MM1 WT) and Markov-model-1 mutant (MM1 MUT), respectively. We use the Markov models of [14] for the second WT and MUT Na channels, which we label Markov-model-2 wild-type (MM2 WT); and Markov-model-2 mutant (MM2 MUT), respectively. We then replace the Na current in the TP06 model by these two different WT and two different MUT models. Finally, we have three different WT models, i.e., the original TP06, MM1 WT, and MM2 WT; and we have two different MUT models, namely, MM1 MUT and MM2 MUT. All the other currents in the original TP06 model are unaltered in our studies below.

Schematic diagrams of MM1 WT and MM2 WT models are shown in the top panel of Fig. 1. The MM1 WT model has nine states: the open state (**O**), the three

closed states (**C1**, **C2**, **C3**), and the five inactivation states (**IF**, **IM1**, **IM2**, **IC2**, **IC3**). The MM2 WT model has eight states: the open state (**O**), the three closed states (**C1**, **C2**, **C3**), and the four inactivation states (**IF**, **IS**, **IC2**, **IC3**). The orange, double-headed arrows indicate transitions between such Markov states; transition rates for the rightward (leftward) transition are given above (below) these arrows, e.g., a_{111} (b_{111}) for the **IC3** $\rightarrow$ **IC2** (**IC2** $\rightarrow$ **IC3**) transition in MM1 WT. Similar schematic diagrams for the MM1 MUT and MM2 MUT models are given in the bottom panel of Fig. 1. The MM1 MUT model has the same number of states as the MM1 WT model, but the transition rates between the Markov states are different. The MM2 MUT model has 12 states: 8 of these are as in the MM2 WT model; in addition, there are 4 bursting states, namely, **BO**, **BC1**, **BC2**, and **BC3**.

The dynamics of transitions between the states of these Markov models and the Na-channel current I_{Na} are given, respectively, by Eqs. (7) and (8) below:

$$\frac{dP_k}{dt} = \sum_{l, l \rightarrow k} \alpha_l P_l - \sum_{l, k \rightarrow l} \beta_l P_k, \quad (7)$$

where l and k label the states **O**, **C1**, **C2**, **C3**, **IC2**, **IC3**, **IM1**, **IM2**, **IF**, **IS**, **BO**, **BC1**, **BC2**, **BC3** (Fig. 1); α_l and β_l are generic labels for forward- and backward-transition rates, respectively;

$$I_{\text{Na}} = G_{\text{Na}} (P_{\text{O}}) (V_m - E_{\text{Na}}), \quad (8)$$

where P_{O} is the probability of the opening of the Na channel.

We employ the values of G_{Na} that are employed either in the original TP06 model [18] or in [19]; specifically, we use

$$G_{\text{Na}} = \begin{cases} 14.838 \text{ nS/pF, TP06, MM2 WT, and MM2 MUT;} \\ 16 \text{ nS/pF, MM1 WT and MM1 MUT.} \end{cases}$$

The major differences between the two MM (WT and MUT) models are as follows. (1) The number of states and the connections between them (see Fig. 1). (2) The MM2 WT model has an Na current with a late component; this is absent in the MM1 WT model. We show below that these differences can have significant effects on single-cell and spiral-wave properties in these models.

D. Numerical simulations

The details of our numerical simulations, such as, the time-marching and finite-difference schemes that we use and the S1-S2 protocol, which we employ to initiate spiral waves, are given in Appendixes A and B. We record the single-cell AP and its morphology, after we have paced the cell with n pulses, each with a constant pacing cycle length (PCL); we use $n = 500$ pulses. We obtain the dynamic action potential duration restitution (APDR) (s1-s1) as follows: (a) we apply 17 pulses with a fixed PCL (s1); then, once the system reaches a steady state, we record the time at which the cell is 90% repolarized; this is the action potential duration (APD₉₀) or simply the APD; we also record the previous diastolic interval (DI). We next obtain the dynamic conduction velocity restitution (CVR) (s1-s1) as follows. We consider a very narrow strip of tissue consisting of 832×10 cells; this is similar to a long cable with a narrow width; we pace it by applying a current stimulus (s1) at one of its ends; we obtain CV from the time that an isopotential line takes to move between two cells, which are separated by a fixed distance. The CVR is the plot of CV versus DI.

To obtain the inactivation and activation properties of MM1 WT, MM2 WT, MM1 MUT, and MM2 MUT Na channels, we use the voltage-clamp-simulation protocol of Ref. [19]. In the activation protocol, we clamp the cell with a voltage V_c , which ranges from the hyperpolarized regime (below the resting membrane potential of an action potential) to the depolarized regime (≈ 50 mV); we do this in steps of 5 mV; the clamping is maintained for a clamping time $t_c = 1$ s. We then record the peak current $I_{\text{peak Na}}(V_c)$ and divide it by the driving force ($V - E_{\text{Na}}$) to obtain the conductance $G(V_c)$, which we normalize to obtain the activation variable $\mathcal{A}$ as follows:

$$\begin{aligned} V_c &= -100 \text{ mV to } 50 \text{ mV, } t = 1 \text{ s;} \\ I_{\text{peak Na}}(V_c) &= \max(P_O) [V_c - E_{\text{Na}}]; \\ G(V_c) &= \frac{I_{\text{peak Na}}}{(V - E_{\text{Na}})}; \\ \mathcal{A} &\equiv \frac{G(V_c)}{G(V_c = 50 \text{ mV})}. \end{aligned} \quad (9)$$

Similarly, for the inactivation protocol, we use a holding potential V_h , ranging between hyper-polarized and the depolarized values, and apply it for ≈ 250 ms; we then apply a test potential $V_t = 0$ mV, record the peak Na current, and then

define the inactivation variable $\mathcal{I}$ as follows:

$$V_c = \begin{cases} V_h = -130 \text{ mV to } -10 \text{ mV, } t < 250 \text{ ms;} \\ V_t = 0 \text{ mV, } t = 250 \text{ ms;} \end{cases}$$

$$I_{\text{peak Na}}(V_c) = \max(P_O) [V_c - E_{\text{Na}}], \quad t > 250 \text{ ms};$$

$$\mathcal{I} \equiv \frac{I_{\text{peak Na}}(V_c)}{I_{\text{peak Na}}(V_c = -130 \text{ mV})}. \quad (10)$$

We calculate recovery from inactivation by using a double-pulse protocol [22], in which the cell is held initially to a holding potential $V_h = -100$ mV and then stepped up to -10 mV, for a duration of 1 s. We now step it back to -100 mV, for a variable time duration t , and then step it up to -10 mV, for 30 ms. We plot versus t the normalized ratio

$$\text{Normalized } I_{\text{Na}} = \frac{I_{\text{Na,max1}}}{I_{\text{Na,max2}}}, \quad (11)$$

where $I_{\text{Na,max}} = I_{\text{Na,max1}}$, when the cell is first stepped to -10 mV for 1 s, and $I_{\text{Na,max}} = I_{\text{Na,max2}}$, when the cell is stepped up to -10 mV for the 30 ms.

We have carried out the following two sets of simulations of electrical-wave dynamics, with certain localized inhomogeneities in an otherwise homogeneous simulation domain. (a) In the first set of simulations we introduce circular (2D) regions with a random distribution of inexcitable obstacles to mimic localised fibrotic patches in Markov-state WT models; an important control parameter here is P_f , the percentage of inexcitable obstacles. (b) In the second set of simulations, we examine electrical-wave dynamics in the presence of a circular patch of mutant cells in an otherwise homogeneous, 2D WT domain.

We calculate the probabilities of the Markov states for Markov-state models. For both wild-type and mutant Na channels, there are three main classes of Markov states, namely, the open states (O, BO), the inactivation states (IF, IS, IM1, IM2, IC2, IC3), and the closed states (C1, C2, C3, BC1, BC2, BC3). The probabilities of these three classes of states are as follows: P_O is the open-state probability; P_I is the sum of probabilities of all the inactivation states; and P_C is the sum of probabilities of all the closed states. In the case of MM1 WT and MM2 WT models, they are as follows:

$$P = \begin{cases} P_O \text{ (MM1 WT and MM2 WT);} \\ P_I = P_{IF} + P_{IM1} + P_{IM2} + P_{IC2} + P_{IC3} \text{ (MM1 WT);} \\ P_I = P_{IF} + P_{IS} + P_{IC2} + P_{IC3} \text{ (MM2 WT);} \\ P_C = P_{C1} + P_{C2} + P_{C3} \text{ (MM1 WT and MM2 WT).} \end{cases}$$

The probabilities of these three main classes of states, in MM1 MUT and MM2 MUT models, are as follows:

$$P = \begin{cases} P_O \text{ (MM1 MUT);} \\ P_I = P_{IF} + P_{IM1} + P_{IM2} + P_{IC2} + P_{IC3} \text{ (MM1 MUT);} \\ P_C = P_{C1} + P_{C2} + P_{C3} \text{ (MM1 MUT);} \\ P_O \equiv P_O + P_{BO} \text{ (MM2 MUT);} \\ P_I = P_{IF} + P_{IS} + P_{IC2} + P_{IC3} \text{ (MM2 MUT);} \\ P_C = P_{BC1} + P_{BC2} + P_{BC3} + P_{C1} + P_{C2} + P_{C3} \text{ (MM2 MUT).} \end{cases}$$

FIG. 2. Na-channel activation $\mathcal{A}$ and the inactivation $\mathcal{I}$, in the models MM1 (WT and MUT) and MM2 (WT and MUT), compared with their TP06 counterparts. (a) Activation and (b) inactivation plots; in the insets, we show the activation- and inactivation-protocol plots for different values of the clamp voltage V_c , for the TP06 model $\mathcal{A} = m_\infty^3$ and $\mathcal{I} = j_\infty \times h_\infty$. (c) Semilog plots the normalized I_{Na} vs time; these plots illustrate the recovery from inactivation for a holding potential of $V_h = -100$ mV for all the five models. (d) Plots of $(\mathcal{A} \times \mathcal{I})$ vs V_m showing the region of V_m in which $\mathcal{A} \times \mathcal{I}$ is large; this is the region in which there is a significant window current [see plots in (e)]. (e) I_{Na} vs V_m plots for all the five models.

III. RESULTS

A. Single-cell results

1. Activation, inactivation, and recovery from inactivation of the Na channel

We begin with a comparison of the activation $\mathcal{A}$ and the inactivation $\mathcal{I}$ in the models MM1 (WT and MUT) and MM2 (WT and MUT) with their TP06 counterparts. Figures 2(a) and 2(b) show the activation and inactivation (see Sec. II C), which depict, respectively, the dependences of $\mathcal{A}$ and $\mathcal{I}$ on V_m for the MM1 WT, MM2 WT, MM1 MUT, MM2 MUT, and TP06 models; for the TP06 model $\mathcal{A} = m_\infty^3$ and $\mathcal{I} = j_\infty \times h_\infty$.

If we contrast the plots of $\mathcal{A}$ in Fig. 2(a), we see that the curves for both MM1 WT and MM1 MUT models lie to the right of, and are less steep than, their TP06, MM2 WT, and MM2 MUT counterparts; hence, activation occurs most slowly (with respect to V_m) in MM1 WT and MM1 MUT models. $\mathcal{A}$ is not significantly different in the case of wild-type (WT) mutant Markov models (MM1 MUT and MM2 MUT). By contrast, in the WT case, Fig. 2(b) shows that the TP06 Na ion channel inactivates early compared to its MM counterparts; also, MM2 WT inactivates at a lower value of V_m compared to MM1 WT; the inactivation curves for MM1 WT and MM2 WT models are shifted (towards positive V_m) compared to this curve in the TP06 model. In Table I, we give, for all the five models, the values of V_m at which complete activation, complete inactivation, and half-maximum activation and half-maximum inactivation in columns 2, 3, 4, and 5, respectively.

To observe clearly the differences between activation and inactivation for all these models, we show, via a plot of $\mathcal{A} \times \mathcal{I}$ versus V_m [Fig. 2(d)], the region of V_m in which there is a window current. We observe that, in the WT case, the TP06 model has a higher window current than MM1 WT and MM2 WT. Note that the window currents for mutant models are significantly longer than their WT counterparts.

We have also calculated the recovery from inactivation for all the models [semilog plots in Fig. 2(c)]. The protocol we use to calculate the recovery from inactivation follows Ref. [22] and is explained in the Sec. II D. This plot shows that, compared to all the models, the Na ion channel in the TP06 model recovers slowly from inactivation as in Ref. [22]. The MM2 WT model recovers much faster than does the

TABLE I. The potential values at which complete activation (column 2), complete inactivation (column 3), half-maximum activation (column 4) and half-maximum inactivation (column 5) occur for the Na channel in all the five models (Fig. 2).

Model	$V_{\mathcal{A}=1}$ (mV)	$V_{1/2, \mathcal{A}=0.5}$ (mV)	$V_{\mathcal{I}=1}$ (mV)	$V_{1/2, \mathcal{I}=0.5}$ (mV)
TP06	2	-36	-116	-84
MM1 WT	60	-24	-90	-61
MM2 WT	-14	-32	-88	-69
MM1 MUT	60	-20	-100	-66
MM2 MUT	-8	-34	-86	-70

FIG. 3. Plots of the probabilities P_I , P_C , and P_O (see text) vs time t for the Na channel in the course of an action potential. Plots for the MM1 (MM2) model are in the top (bottom) panel; the blue and red curves are for WT and MUT models, respectively. We obtain these plots by pacing a single cell with a pacing-cycle length $PCL = 3000$ ms in MM1 and MM2 models for both WT and MUT cases (plots for the $n = 501$ stimulation). The plots in the insets show the sudden opening of the Na channel in the mutant cases because of delayed inactivation and closing.

MM1 WT model. The mutant Markov models show differences compared to their wild-type counterparts after 1 ms.

The above Na ion-channel activation, inactivation and recovery from inactivation properties affect the dynamics of the Na ion-channel current.

Our results for the two Markov-state models are in agreement with those shown in Fig. 2 of Refs. [16,19].

2. Probabilities of the Markov states

Figure 3 shows plots of P_O , P_I , and P_C versus time t for the Na channel in the course of an action potential for MM1 (MM2) models in the top (bottom) panel; the blue and red curves are for WT and MUT models, respectively. We obtain these plots by pacing a single cell with $PCL = 3000$ ms. By comparing the blue curves in Figs. 3(a), 3(b), 3(d), and 3(e), we find that the duration for which the Na channel is in the inactivation or closed states, i.e., the time interval during which $P_I = 1$ and $P_C = 0$ (inactivation state) or $P_I = 0$ and $P_C = 1$ (closed state), is approximately the same in MM1 WT and MM2 WT models. In contrast, the duration for which P_O is significantly greater than 0 differs in MM1 WT and MM2 WT models [compare the blue curves in Figs. 3(c) and 3(f)]; this duration, measured by the full width at half maximum (FWHM) of P_O , is $\simeq 0.37$ ms and $P_{O,\max} \simeq 0.17$, for MM1 WT, and $\simeq 0.13$ ms and $P_{O,\max} \simeq 0.28$, for MM2 WT. The blue curves in the insets of Figs. 3(c) and 3(f) show that, in the MM1 WT model, there is no late-Na current because $P_O = 0$ in the repolarization phase of the action potential

(AP); in contrast, the MM2 WT model yields $P_O \simeq 0.0003$ at $t \simeq 350$ ms, which demonstrates that the Na channel opens in the repolarization regime of the AP. In the MUT cases, the time duration for which the Na channel is in the inactivation or closed states is prolonged compared to that in the WT cases [see Figs. 3(a), 3(b), 3(d), and 3(e)]; from the insets of these figures we see that P_I decreases slightly below 1 [there are corresponding increases in P_O and P_C [see Figs. 3(c) and 3(f)], for $360 \text{ ms} \lesssim t \lesssim 1110 \text{ ms}$ in MM1 MUT and $360 \text{ ms} \lesssim t \lesssim 1700 \text{ ms}$ and MM2 MUT. The duration for which the Na channel is in the inactivation state $P_I = 1$ and $P_C = 0$, for MM2 MUT, is much longer than that in MM1 MUT. We find the following FWHMs: for P_I FWHM $\simeq 1729.2$ ms (MM2 MUT) and $\simeq 1200.25$ ms (MM1 MUT); for P_C FWHM $\simeq 1721.2$ ms (MM2 MUT) and $\simeq 1176.2$ ms (MM1 MUT). $P_{O,\max}$ is markedly different in both MUT models: $\simeq 0.4796$ (MM2 MUT) and $\simeq 0.0861$ (MM1 MUT); and the FWHM of P_O is $\simeq 0.14$ ms (MM2 MUT) and $\simeq 1.03$ ms (MM1 MUT).

3. Action potential, APDR, and CVR

We pace a single cell with the following three different values of PCL: high frequency (PCL = 300 ms), intermediate frequency (PCL = 650 ms), and low frequency (PCL = 1000 ms). We present the steady-state AP and the Na current I_{Na} at the top panel of Figs. 4(A)–4(C) (for PCL = 1000 ms), for the three WT models; and we compare the morphological properties of the APs of these models in Table II.

FIG. 4. Plots of action potentials, the fast Na current $I_{Na,f}$, and the late Na current $I_{Na,L}$. Top panel: cell paced for $PCL = 1000$ ms for $n = 501$ stimulations for TP06, MM1 WT, and MM2 WT models (plots for the $n = 501$ stimulation). Bottom panel: cell paced for $PCL = 3000$ ms for MUT models and comparing MM1 WT with MM1 MUT and MM2 WT with MM2 MUT (plots for the $n = 501$ stimulation). Note that the late opening of the mutant Na channel in the repolarization regime causes a release of $I_{Na,L}$ that leads, in turn, to early afterdepolarizations (EADs) in the AP for mutant models.

4. $PCL = 1000$ ms

Given the differences in the activation profiles in Figs. 2(c), 2(d) and the plots of P_O for the MM models in Figs. 3(c), 3(f) we observe that (a) the times at which the Na channels open are different in all the three WT models; and (b) the amplitude of I_{Na} is comparable in MM2 WT (-312.74 pA/pF) and TP06 (-300.43 pA/pF) models, but it is significantly lower in the

MM1 WT model (-144 pA/pF) as we show in Fig. 4(b). These differences in the amplitude of I_{Na} affect the maximum voltage and the upstroke-velocity of the AP (Table II). The upstroke velocities for TP06, MM1 WT, and MM2 WT models are markedly different (Table II). Also, there is the late component of the Na current $I_{Na,L}$ [Fig. 4(c)] in the case of MM2 WT; this component is clearly absent in TP06 and MM1 WT models. P_O becomes significant at ≈ 350 ms in the MM2 WT model [Fig. 3(f)], so the APD for this model is larger than its counterparts in the TP06 and MM1 WT models [see Fig. 4(c) and Table II].

5. $PCL = 300$ ms

As we decrease PCL, say to 300 ms, we find that both $I_{Na,max}$ (the maximal value of $-I_{Na}$) and the upstroke velocity in the MM2 WT model increase relative to their counterparts in the TP06 model as we show in Table II (contrast this with our results for $PCL = 1000$ ms). These increases occur principally because $P_{O,max}$ is higher in the MM2 WT model than in the TP06 model.

6. $PCL = 3000$ ms, MUT Na channel

In Figs. 4(d), 4(e), and 4(f), we show, respectively, plots of V_m , $I_{Na,f}$, and $I_{Na,L}$ versus time t ; we use dashed curves for the MM1 MUT (blue) and MM2 MUT (red) models and the illustrative value $PCL = 3000$ ms. Clearly, the MM1 MUT

TABLE II. Characteristic properties of the action potentials in TP06, MM1 WT, and MM2 WT models. These data are for three representative cases: low-frequency ($PCL = 1000$ ms), intermediate-frequency ($PCL = 650$ ms), and high-frequency ($PCL = 300$ ms) pacing.

PCL (ms)	Model	$I_{Na,max}$ (pA/pF)	V_{max} (mV)	$\frac{dV}{dt}_{max}$ (mV/ms)	APD (ms)
300	TP06	-177.19	23.42	227.97	218.76
	MM1 WT	-82.23	21.17	81.76	219.66
	MM2 WT	-252.13	18.56	256.8	226.76
650	TP06	-298.19	37.17	349.94	291.56
	MM1 WT	-127.6	32.78	128.8	292.36
	MM2 WT	-280.98	23.74	280.79	304.6
1000	TP06	-312.74	39.82	373.65	302.12
	MM1 WT	-144.46	36.58	146.18	302.64
	MM2 WT	-300.43	25.11	300.49	314.84

FIG. 5. Restitution plots for the TP06, MM1 WT and MM2 WT models. (a) Single-cell APDR (profiles for TP06 and MM1 WT models lie close to each other, but the MM2 WT curve lies above these) and (b) the dynamic CVR, for a one-dimensional cable of cells (640×10). The slopes of the profiles are given in (c) for the APDR and in (d) for the CVR; in all these three models, the maximal slope of the APDR profile is greater than 1; the CVR profiles in MM1 WT and MM2 WT models do not depend sensitively on DI over the range of values in these plots. The solid lines are calculated for the same diffusion constant D ; for the MM1 WT and MM2 WT models this yields steady-state CVs of 40.41 and 54.89 cm/s, respectively, which are not in the normal range (for the myocardium) $\simeq 60$ –75 cm/s; if we increase D , for the MM1 WT and MM2 WT models (see text) CV can be brought to this normal range, as we show by the dashed-line plots.

and MM2 MUT APs in Fig. 4(d) show early afterdepolarizations (EADs) [20,21], insofar as their APs are prolonged considerably relative to the APs for MM1 WT and MM2 WT models, because of the failure of inactivation near the repolarization region (insets in Fig. 3).

7. APDR and CVR (WT)

For the TP06, MM1 WT, and MM2 WT models, we present plots of the single-cell APDR [Fig. 5(a)] and the dynamic CVR [Fig. 5(b)], for a one-dimensional cable of cells. The APDR profiles for TP06 and MM1 WT lie close to each other, but the MM2 WT curve lies above these, because of the late current component $I_{Na,L}$ (see above). The slopes of the APDR and CVR profiles are given, respectively, in Figs. 5(c) and 5(d). Note that, in all these three models, the maximal slope of the APDR profile > 1 (it is highest in the MM1 WT model). The Na channel determines the upstroke velocity at the cellular level; therefore, this channel plays an important role in determining CV, in cardiac tissue, and also CVR plots [Fig. 5(b)]. From these plots, we find that, for TP06, MM1 WT, and MM2 WT models, CV is nearly independent of DI, for large DI; the ranges spanned by CV

are 60.51–70.55 cm/s (TP06), 35.5–40.4 cm/s (MM1 WT), and 51.43–54.89 cm/s (MM2 WT), for DI in the interval 90–900 ms; and the saturation values of CV are $\simeq 70.55$ cm/s (TP06), $\simeq 40.41$ cm/s (MM1 WT), and 54.89 cm/s (MM2 WT). In the human myocardium, CV is $\simeq 60$ –75 cm/s [18,22]. To obtain CV in this physiological range, we must increase the diffusion constant D in both MM1 WT and MM2 WT models; we find that, if we multiply D by 2.915 (MM1 WT) and 1.299 (MM2 WT), then the saturated value of CV is $\simeq 64.65$ cm/s (MM1 WT) $\simeq 71.75$ cm/s (MM2 WT); these multiplicative scale factors can be obtained by noting that $CV \propto \sqrt{D}$ [2,7] and by using the saturated CV value in the TP06 model. With these changes in D , CV can be brought to a physiologically realistic value; but its variation is small: 60.69–64.65 cm/s (MM1 WT) and 62.34–71.75 cm/s (MM2 WT) over the DI range of 90–900 ms.

B. 2D results

We have explored differences between the TP06, MM1, and MM2 models at the single-cell and the cable levels. We now compare spiral- and scroll-wave dynamics in these

FIG. 6. Pseudocolor plots of the transmembrane potential V_m illustrating the spatiotemporal evolution of spiral waves in all the five models. WT models are shown in (a) TP06, (b) MM1 WT, and (c) MM2 WT; in the MM1 WT (MM2 WT) model the spiral wave is stable (unstable). MUT models are shown in (d) MM1 MUT and (e) MM2 MUT. The formation of type-3 EADs (see text) leads to backward propagation in the MM2 MUT; by contrast, the type-2 EAD in the MM1 MUT model does not lead to such backward propagation. However, these EADs create, at the cellular level, dynamical heterogeneities, far from the stable spiral core, as shown in (d); this leads to spiral break up in a homogeneous MM1 MUT simulation domain. The complete spatiotemporal evolution of the spiral waves of MM1 MUT and MM2 MUT is shown in the movie M3 in Ref. [17].

models by carrying out detailed numerical simulations in 2D (Sec. III B) and 3D (Sec. III E) domains.

C. Wild-type Na channel

We contrast, in the top panel of Fig. 6, spiral waves in these three models, with $D = 0.00154 \text{ cm}^2/\text{ms}$. We find that spiral waves in TP06 and MM1 WT are stable and they rotate with frequencies $\omega = 4.75$ and 4.25 Hz , respectively; in particular, the low value of CV (40.41 cm/s), in the MM1 WT model with $D = 0.00154 \text{ cm}^2/\text{ms}$, does not alter the spiral-wave dynamics qualitatively. By contrast, in the MM2 WT model, the spiral wave is unstable and exhibits transient breakup; it is not possible to isolate a single cause for this break up, but the late Na current $I_{\text{Na,L}}$ [Fig. 4(c)] plays an important role in this instability; we have checked that, by increasing β_{12} , we can reduce the magnitude of this late current and thus suppress spiral-wave turbulence (the spiral meanders but does not break up into multiple spirals as we show in movie M0 in Ref. [17]).

We have carried out another set of studies in 2D simulation domains, with the values of D scaled up to $D \times 2.915$ (MM1 WT) and $D \times 1.299$ (MM2 WT), to bring the values of CV close to the range of values in human ventricular tissue [18]. These scaled values of D do not change our qualitative results about spiral-wave stability (TP06 and MM1 WT) or their breakup (MM2 WT) (for details see Appendix C). However, the spiral-arm width increases when we scale up the value of D (see Fig. 13, Appendix C and movie M1 in Ref. [17]); furthermore, because CV increases when we scale up D , the spiral-wave rotation frequency ω also increases with D . Henceforth, in our 2D and 3D simulations we use the same fixed value $D = 0.00154 \text{ cm}^2/\text{ms}$ for all three models (TP06, MM1 WT, and MM2 WT).

We employ the S1-S2 protocol to initiate spiral waves in all these models (Sec. II). The pseudocolor plots of V_m in Fig. 7 show that the spiral-wave activity in the TP06 and MM1 WT models is independent of the time τ_{S2} , at which the S2 pulse is applied after the S1 pulse (we use $560 \text{ ms} \leq \tau_{S2} \leq 620 \text{ ms}$). By contrast, in the MM2 WT model, we observe spiral-wave breakup for $\tau_{S2} = 560 \text{ ms}$ and 580 ms until the end of our simulation, i.e., 10 s ; but spiral-wave activity vanishes for $\tau_{S2} = 600 \text{ ms}$ at $\approx 5.5 \text{ s}$ and for $\tau_{S2} = 620 \text{ ms}$ at $\approx 6.8 \text{ s}$ (Fig. 7 and movie M2 in Ref. [17]).

Spiral-wave dynamics in the MM2 WT model depends on the time τ_{S2} at which we initiate the S2 pulse. It behooves us, therefore, to examine whether obstacles (or conduction inhomogeneities) affect spiral-wave activity in the MM1 WT and MM2 WT models, for it has been shown, for HH-type models for cardiac tissue, that spiral-wave dynamics depends sensitively on the position, size, and shape of such obstacles [3,4,23,24]. Our obstacles consist of inexcitable points that are distributed randomly within a circular region of radius R ; P_f is the percentage of the area of the circle that has inexcitable obstacles. Given our experience with studies of spiral-wave dynamics with such obstacles in HH-type models, we expect that, as P_f increases, such an obstacle should anchor a spiral wave [25,26]. Therefore we investigate the dependence of spiral-wave dynamics on P_f and R in the MM1 WT and MM2 WT models and compare this with its counterpart in the TP06 model, for different values of τ_{S2} . Illustrative plots from our simulations are shown in Fig. 8.

We find that, for the TP06 and MM1 WT models, the anchoring of the spiral wave depends on R and on P_f , but not on τ_{S2} . The time period T of the anchored spiral increases with R and P_f as we show in Fig. 9(a); but T decreases for lower percentages (e.g., $P_f = 30\%$) in TP06 and MM1 WT models at large values of R [Fig. 9(a)]. The interaction of the tip of the spiral wave with the obstacle is complicated. In particular, this depends on how much of the region, inside the circular patch, is excitable. For low values of P_f , this excitable region forms a tortuous but spanning cluster (in the sense of percolation theory [27]), so the tip of the spiral propagates inside the obstacle, the wave of activation is slightly deformed there, but then it re-emerges into the homogeneous part of the simulation domain. If P_f is large, the excitable region can still be tortuous, but it does not form a spanning cluster, so the tip of the spiral rotates around the obstacle, and is anchored to it, but does not propagate inside it. To quantify the effect of our obstacle on the spiral wave we calculate $\delta T \equiv (T - T_0)$, where T is the time period (or inverse of the rotation frequency ω), at a given set of values of P_f and R , T_0 is the time period (or inverse of the corresponding frequency ω_0) with $P_f = 100\%$ for the same value of R . Clearly, T must depend on P_f and R . The plots in Figs. 9(b) and 9(d) show, for TP06 and MM1 WT models, the dependence of δT on R for different values of P_f . Given these plots, we identify three regions, namely, (i) $\delta T < 0$, i.e., $\omega > \omega_0$, (ii) $\delta T > 0$,

FIG. 7. Pseudocolor plots of the transmembrane potential V_m illustrating the spatiotemporal evolution of spiral waves for different values of τ_{S2} , the time interval between the S1 and S2 impulses (see Appendix A) for the three WT models. We show in (a) TP06 and (b) MM1 WT models at 5.9 s after spiral-wave initiation; and (c) the MM2 WT model at 6.9 s after such initiation. Clearly, the spatiotemporal evolution of the spiral waves in the TP06 and MM1 WT models are independent of τ_{S2} , in the range of values investigated here, but not the case with the MM2 WT model. The spatiotemporal evolution of the spiral waves for different τ_{S2} of MM2 WT is shown in movie M2 in Ref. [17].

i.e., $\omega < \omega_0$, and (iii) $\delta T = 0$, i.e., $\omega = \omega_0$. If $\delta T > 0$, then the frequency $\omega \sim T^{-1}$, for a given pair (R, P_f) , is less than $\omega_0 \sim T_0^{-1}$ (for $R, P_f = 100\%$); this may occur if the spiral core penetrates the obstacle because of a spanning cluster of excitable regions inside the obstacle. In Figs. 9(c) and 9(e), we show different colored regions in the (R, P_f) plane for TP06 and MM1 WT models, respectively: light blue indicates an increase in ω relative to ω_0 (caused by penetration of the spiral core); light green is for a decrease in ω relative to ω_0 (accompanied by penetration of the spiral core); yellow indicates no penetration of the spiral core into the obstacle; dark blue depicts regions in which there is no change in ω relative to ω_0 even though the spiral core penetrates into the obstacle.

For the MM2 WT model, the minimum size $R_{\min}$ for spiral anchoring is large, compared to that in TP06 and MM1 WT model; we find $R_{\min} \simeq 1.875$ cm (movie M5 in Ref. [17]). The threshold percentage in the MM2 WT case is $P_{f,\min} \simeq 50\%$. Once we reach the values $R_{\min}$ and $P_{f,\min}$ required for anchoring, the spiral activity is independent of τ_{S2} , as we show in the fourth row of Fig. 8. The dependence of the spiral rotation time period T on R , for different values of P_f , is shown in Fig. 9(a). Stability diagrams for the spiral-wave activity, in the presence of localized, inexcitable obstacles distributed within a circular region of radius R , are shown in the (R, τ_{S2}) plane, for different values of P_f in the MM2 WT model, in Fig. 10; brown, green, and blue denote regions with an anchored spiral, spiral breakup, and no activity, respectively.

D. Mutant Na channel

The mutant Na channel fails to inactivate completely in the MM1 MUT and MM2 MUT models; this leads to prolonged EADs, as we have shown in Sec. III A 1 and Fig. 4. We find that two of the types of EADs that have been discussed in Ref. [20] occur in both these MUT models: there is a single

EAD (of type 2 in the nomenclature of Ref. [20]), in the MM1 MUT model, and an oscillatory EAD (roughly of type 3 in the nomenclature of Ref. [20]), in the MM2 MUT model. These two types of EADs affect the wave dynamics differently, as we demonstrate explicitly by simulating plane-wave propagation in our 2D domain, but with all mutant myocytes. We observe backward propagation of the plane wave in the MM2 MUT model because of the oscillatory EADs; by contrast, there is no such backward propagation in the MM1 MUT model. If we initiate a spiral wave in both these models, then (a) in the MM1 MUT model, we get almost-instantaneous far-field breakup away from the core, but the mother rotor is unaffected and (b) in the MM2 MUT model, we obtain almost-instantaneous spiral break-up [bottom panels of Figs. 6(d) and 6(e)]. The complete spatiotemporal evolution of such spiral-wave dynamics, for both these cases, is shown in movie (M3) in Ref. [17].

Although there are several studies of the effects of different types of inhomogeneities on spiral-wave dynamics in mathematical models for cardiac tissue (see, e.g., Refs. [3,4,23,24] and references therein), to the best of our knowledge there has been no study, based on Markov-state models, of an inhomogeneity comprising mutant myocytes in a background of wild-type myocytes. Therefore we present a representative study of spiral-wave dynamics in the presence of a clump of only mutant cells, of radius $R = 1.125$ cm, embedded in a background of wild-type cells. We then explore the possibility of spiral-wave formation via high-frequency stimulation by pacing the simulation domain from the left boundary (pacing frequency 3.7 Hz). We find that, in the MM1 MUT model, no spiral wave forms [Fig. 11(a)]; by contrast, in the MM2 MUT model a spiral wave forms [Fig. 11(b)]. [The spatiotemporal evolution of these waves is shown in movie M10 in Ref. [17].] This qualitative difference arises because of the different types of EADs (discussed above) in MM1 MUT and MM2 MUT models.

FIG. 8. Pseudocolor plots of the transmembrane potential V_m illustrating the spatiotemporal evolution of spiral waves in the presence of inexcitable obstacles for different values of P_f and different τ_{S2} . The pseudocolor plots in the same row are for a given model, and the different columns depict different percentage P_f of inexcitable obstacles. Pseudocolor plots in the row (i) depicts the wave dynamics for the TP06 with inexcitable obstacle radius $R = 1.375$ cm, which in row (ii) depicts MM1 WT with $R = 1.375$ cm, which in row (iii) depicts MM2 WT with $R = 1.375$ cm and in row (iv) depicts MM2 WT models with $R = 1.875$ cm. In the first column, the pseudocolor plots (a), (e), (i), and (m) show the spiral wave dynamics for $P_f = 30\%$. In second column the pseudocolor plots (b), (f), (j), and (n) show the spiral wave dynamics for $P_f = 50\%$. In the third column, the pseudocolor plots (c), (g), (k), and (o) show the spiral wave dynamics for $P_f = 70\%$. In the fourth and last column, the pseudocolor plots (d), (h), (l), and (p) shows the spiral wave dynamics for $P_f = 100\%$. The spatiotemporal evolution of the spiral waves in the presence of inexcitable obstacles for two representative radii ($R = 1.375$ and 1.875 cm) for the MM2 MUT model is shown in movies M5 and M4 in Ref. [17].

E. 3D results

We give an illustrative study of scroll waves in 3D TP06, MM1 WT, and MM2 WT models. These waves are shown

via color isosurface plots of the transmembrane potential V_m in Figs. 12(a), 12(b), and 12(c), respectively, for both a homogeneous domain (top panel) and with localized obstacles

FIG. 9. The dependence of the time period T of the anchored spiral wave on the radius R and percentage of fibrosis P_f . (A) Plots of T versus R for different values of P_f for TP06, MM1 WT and MM2 WT models; note spiral anchoring starts around $R \simeq 1.875$ cm for the MM2 WT model. [(b) and (d)] Plots of the change in time period δT vs R , (obtained from five recording points in the domain of which one grid point is in the region with heterogeneity) for TP06 and MM1 WT models (T_0 is the time period for a completely inexcitable obstacle ($P_f = 100\%$)), for different P_f . If $\delta T > 0$, then the frequency $\omega \sim T^{-1}$, for a given pair (R, P_f) , is less than $\omega_0 \sim T_0^{-1}$ (for $R, P_f = 100\%$); this may occur if the spiral core penetrates the obstacle because of a spanning cluster of excitable regions inside the obstacle. In (C) and (E) we show different regions in the (R, P_f) plane for TP06 and MM1 WT models, respectively, with the following the color code: **Light Blue**: an increase in ω relative to ω_0 (caused by penetration of the spiral core). **Light Green**: decrease in ω relative to ω_0 (accompanied by penetration of the spiral core); (R, P_f) . **Yellow**: No penetration of the spiral core into the obstacle. **Dark Blue**: No change in ω relative to ω_0 even though the spiral core penetrates into the obstacle.

[$P_f = 10\%$ (middle panel) and $P_f = 50\%$ (bottom panel)]. In a homogeneous domain, scroll waves are stable in TP06 and MM1 WT models, but not in the MM2 model. An inexcitable obstacle, with $P_f = 10\%$, has no significant impact on scroll waves in TP06 and MM1 WT models. An increase in P_f , say to $P_f = 50\%$, leads to an anchoring of the scroll waves at the obstacle (as in the study of inexcitable obstacles in Ref. [6]). For the MM2 model, with $P_f = 10\%$, scroll-wave break-up is enhanced; but for $P_f = 50\%$, the scroll wave gets anchored

to the obstacle. The spatiotemporal evolution of these scroll waves is shown in movie M10 in Ref. [17].

F. Na ion-channel Markov Model selection

It is natural to ask the following question: Which mathematical model should we choose from such Markov-state models for cardiac tissue? We begin with a list of desiderata for a good model for the Na wild-type ion channel.

FIG. 10. Stability diagrams for spiral-wave activity, in the presence of localized, inexcitable obstacles distributed within a circular region of radius R , for different values of P_f , in the MM2 WT model. (a) $P_f = 30\%$, (b) 50% , (c) 70% , and (d) 100% . Color code: brown, green, and blue show regions with an anchored spiral, spiral breakup, and no activity, respectively.

FIG. 11. Pseudocolor plots of the transmembrane potential V_m illustrating the spatiotemporal evolution of electrical-activation waves when there is a circular clump of mutant cells. The clump radius $R = 1.125$ cm (shown via a black circle); this clump is surrounded by wild-type (WT) cells, and the simulation domain is paced from the left boundary (pacing frequency 3.7 Hz). (A) MM1 MUT model (no spiral wave forms) and (B) MM2 MUT model (a spiral wave forms). For the complete spatiotemporal evolution movie see movie M10 in Ref. [17]. The qualitative difference between (a) and (b) arises because of the different types of EADs in MM1 MUT and MM2 MUT models.

(1) The model must reproduce faithfully the experimental Na ion-channel properties such as activation, inactivation, and recovery from inactivation. Specifically, the Na ion channel should exhibit slow-recovery dynamics, which is observed in human-ventricular Na ion channels [18,43].

(2) The model must reproduce the baseline conduction velocity of the normal plane-wave propagation velocity observed in human ventricular tissue.

(3) After the inclusion of the Na ion-channel formulation in the new model, spiral-wave dynamics, in a 2D simulation domain, should not be altered significantly. In particular, if the parent model displays a rigidly rotating spiral wave, then, the new model should also exhibit such a rotating wave with approximately the same value for the spiral-rotation frequency.

We now check which one of the two wild-type Markov models, MM1 WT, and MM2 WT, have these properties. We have shown above that, spiral-wave dynamics, in the 2D MM2 WT model, shows transient breakup with meandering; by contrast, the 2D MM1 WT model shows a stably rotating spiral wave that is similar to the one in the TP06 model, for the normal parameter values (see Fig. 7). Moreover, we have demonstrated that the Na channel in the MM1 WT model recovers more slowly than its counterpart in the MM2 WT model [Fig. 2(c)]. It has been noted in Ref. [18] that the slow recovery of the Na ion channel suppresses wave instabilities that lead to spiral-wave breakup. Also, from the computational perspective, runtime cost of MM1 Markov model is much lower than that of the MM2 Markov model (see Table S2 in Ref. [17]). On balance, then, we propose that the MM1 WT Na Markov model should be selected compared to the MM2 WT model.

IV. DISCUSSION AND CONCLUSIONS

Earlier studies of Markov models for cardiac myocytes have focused on the effects of mutations in subunits of Na and K channels in the context of the Brugada and LQT syndromes [10,11,28,29]; these studies have elucidated the effects of changes in the kinetic properties of these ion channels, and

their consequences, such as the prolongation of the APD, which leads, in turn, to EADs. Also, Markov models have been used to assess the importance of a particular functionality of an ion channel, e.g., the role of I_{Ks} on AP repolarization [30]. Furthermore, Markov models have been used to investigate the activation and inactivation properties of Na, K, and Ca ion channels as, e.g., in Refs. [31–34]. In addition, some studies have focused on therapeutics and drug-channel interactions [13–15], from the cellular to the anatomically realistic tissue levels.

We have investigated, from cellular to tissue levels, the differences in kinetic properties of Na channels in TP06, MM1 (WT and MUT), and MM2 (WT and MUT) models. We have shown that Na channels in TP06 and MM2 (WT and MUT) models are activated faster, with respect to V_m , than their counterparts in the MM1 (WT and MUT) models; also the inactivation of these channels is faster in the TP06 model than in MM1 (WT and MUT) and MM2 (WT and MUT) models. These differences lead to different times of openings of the Na channel and the amplitudes of $I_{Na,f}$ are completely determined by the amplitude of P_O in the MM models. These changes in the amplitudes of $I_{Na,f}$, $I_{Na,L}$, and the activation-inactivation dynamics lead to disparate CVR and maximal CVs in cable simulations. To the best of our knowledge, our study is the first to compare spiral-wave dynamics in different Markov models for the Na (WT and MUT) ion channels in realistic mathematical models for cardiac tissue. We have carried out *in silico* studies, in both homogeneous simulation domains and domains with inhomogeneities, to compare and contrast spiral- and scroll-wave dynamics in five different models for cardiac tissue (Hodgkin-Huxley type, TP06 model [18], and Markov-state models such as MM1 WT and MM2 WT, for the WT Na channel, and MM1 MUT and MM2 MUT, for the mutant Na channel [14,19]). Our study explores the sensitive dependence of spiral- and scroll-wave dynamics on these five models and the parameters that define them. We also examine the control of spiral-wave turbulence in these models. To the best of our knowledge, such a comparative study of wave dynamics in HHM and Markov-state models has not been carried out hitherto. In our opinion, such a comparison is even more valuable than the comparison of single-cell properties of models for cardiac myocytes. We hope our study will lead to more comparisons of wave dynamics in different mathematical models for cardiac tissue and in *in vitro* experiments. Furthermore, we have carried out a detailed parameter-sensitivity study, principally for the WT models by using multivariable linear regression (see Appendix E).

We have listed desiderata for a good model for the Na wild-type ion channel; and we have then proposed that the MM1 WT Na Markov model should be selected compared to the MM2 WT model.

We mention some of the limitations of our study. We have studied the differences in Na ion-channel modeling, which is important in the context of the LQT syndrome; but we have not carried out such a study for Kr-channel modeling, as mutations in the Kr channel also leads to the LQT syndrome. Given our computational resources, we have considered a few, illustrative Markov-state models for Na channels; many more such Markov-state models have been developed for the Na

FIG. 12. Color isosurface plots of the transmembrane potential V_m illustrating scroll waves in (a) TP06, (b) MM1 WT, and (c) MM2 WT models. The isosurfaces lie between -10 and 30 mV in both the homogeneous domain [top panel (i)], and with localized obstacles ($P_f = 10\%$ [middle panel (ii)], $P_f = 50\%$ [bottom panel (iii)]); these illustrative plots are at $t = 2$ s. In a homogeneous domain, scroll waves are stable in TP06 and MM1 WT models, but not in the MM2 model. Note that the scroll wave is anchored to the obstacle with $P_f = 50\%$ in the MM2 model. For the spatiotemporal evolution of these scroll waves, see movies M6–M8 in Ref. [17].

channel [12,35]. Also, we have used a single base model, i.e., TP06 model upon which we build the Markov-state models (MM1 WT, MM1 MUT, MM2 WT, and MM2 MUT); other base models, e.g., the O’Hara-Rudy model [36], can be used. A comprehensive comparison of all these models lies beyond the scope of this paper. We do not use an anatomically realistic simulation domain [37], with information about the orientation of muscle fibers [6,38]; and we use a monodomain description for cardiac tissue. These considerations lie beyond the scope of this paper. We note, though, that the study of Refs. [39,40] has compared results from monodomain and bidomain models and has shown that the differences between them are small.

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Author contributions. Conceived and designed the study: M.K.M., A.R.N., and R.P. Performed the simulations: M.K.M. Analyzed the data: M.K.M., A.R.N., and R.P. Contributed analysis: M.K.M., A.R.N., and R.P. Wrote the paper: M.K.M. and R.P.

APPENDIX A: NUMERICAL IMPLEMENTATION AND THE PROTOCOLS USED FOR OUR STUDY

For our single-cell simulations, we use the Rush-Larsen method to solve Eq. (5) for the HHM; for the MM Eq. (6),

we use the implicit trapezoidal method of Ref. [13] and the forward-Euler method for Eq. (1). In our 2D tissue simulations for Eq. (4), we use a square domain with $N \times N$ grid points, a fixed space step of size $\Delta x = 0.025$ cm, and a time step $\Delta t = 0.02$ ms; in 3D, we use a slab domain (see below). The accuracy of the numerical scheme is tested and is reported in Appendix B.

In the case of 2D and 3D simulations, for the homogeneous tissue we consider D to be a scalar; we use $D = 0.00154$ cm²/ms, as in Ref. [18]; this yields a maximum plane-wave conduction velocity 70 cm/s, which is in the biophysically reasonable range for human ventricular tissue [22]. For the Laplacian in Eq. (4), we use five-point and seven-point stencils, respectively, in 2D and 3D. We impose no-flux

TABLE III. The various ionic currents in the TP06 model [18]; the symbols used for the currents follow [18].

I_{Na}	fast inward Na^+ current
I_{CaL}	L-type inward Ca^{++} current
I_{to}	Transient outward current
I_{Ks}	Slow delayed rectifier outward K^+ current
I_{Kr}	Rapid delayed rectifier outward K^+ current
I_{K1}	Inward rectifier outward K^+ current
I_{NaCa}	Na^+/Ca^{++} exchanger current
I_{NaK}	Na^+/K^+ pump current
I_{pCa}	plateau Ca^{++} current
I_{pK}	plateau K^+ current
I_{bNa}	background inward Na^+ current
I_{bCa}	background inward Ca^{++} current

boundary conditions. When we study the effects of heterogeneities, we introduce, in a localized region of our simulation domain, a patch of inexcitable cells, which are decoupled from adjoining cells (effectively, $D = 0$ in this patch).

Regarding the domain size in our 2D studies, we use two representative square domains, namely, one with 1024×1024 grid points, for our spiral-wave studies, and another with 512×512 grid points, when we pace the simulation domain along an edge. In our studies of scroll-wave dynamics we use a 3D slab domain with $1024 \times 1024 \times 40$ grid points ($25.6 \text{ cm} \times 25.6 \text{ cm} \times 1 \text{ cm}$). We initiate spiral and scroll waves in such domains by using the following S1-S2 cross-field protocol, with stimuli amplitudes of 150 pA/pF and durations of 3 ms . We allow a plane wave (S1) to propagate in the domain along a particular direction; as it propagates, we start another plane wave (S2), in a direction perpendicular to the S1 wave; this results in a conduction block and, eventually, the formation of a spiral wave (2D) or scroll wave (3D). We vary the time interval τ_{S2} between the S1 and S2 impulses to study the sensitive dependence of the spiral-wave dynamics on τ_{S2} .

APPENDIX B: SIZE OF THE DOMAIN AND NUMERICAL CONVERGENCE ANALYSIS

In our numerical studies of 2D and 3D tissue, the domain sizes are 1024×1024 ($25.6 \text{ cm} \times 25.6 \text{ cm}$) and $1024 \times 1024 \times 40$ ($25.6 \text{ cm} \times 25.6 \text{ cm} \times 1 \text{ cm}$), respectively. We employ a square domain, with edges that have a length that is larger than the average linear size of a human heart. We use this large simulation domain, as in other earlier numerical investigations [4,18,48], to suppress the absorption of spiral waves at the boundaries of our simulation domain (the smaller the domain, the more common is such absorption). We can use a simulation-domain size that is of the order of the linear size of a typical human heart; however, to obtain, qualitatively, the same, spiral-wave dynamics with such a domain, we must employ a scaling factor as has been recommended in Refs. [49–52]. Similar comments apply to our 3D simulations. We choose the radius of the circular inhomogeneity as follows: we begin with a radius that is just enough to lead to spiral-wave anchoring; we then increase this radius to obtain the dependence of the frequency of rotation of the anchored spiral on the radius.

We test the accuracy of the numerical scheme we use for all the models by checking the convergence of CV with different values of Δx and Δt . In particular, we calculate CV in a cable of dimension 832×10 and consider the following two cases: (i) $\Delta x = 0.025 \text{ cm}$ fixed and Δt decreasing from $\Delta t = 0.03 \text{ ms}$ to $\Delta t = 0.02 \text{ ms}$; and (ii) $\Delta t = 0.02 \text{ ms}$ fixed and Δx decreasing from $\Delta x = 0.025 \text{ cm}$ to $\Delta x = 0.0175 \text{ cm}$. For the TP06 model and case (i), the decrease in Δt leads to a decrease in CV by $\simeq 1.7\%$; in case (ii), the decrease in Δx leads to an increase in CV by $\simeq 3.7\%$. In the MM1 model and case (i), the decrease in Δt leads to a decrease in CV by $\simeq 1.2\%$; in case (ii), the decrease in Δx leads to an increase in CV by $\simeq 3.1\%$. Furthermore, in the MM2 model and case (i), the decrease in Δt leads to a decrease in CV by $\simeq 0.2\%$; in case (ii), the decrease in Δx leads to an increase in

FIG. 13. Pseudocolor plots of the transmembrane potential V_m illustrating the spiral wave dynamics in the tissue with two different values of the diffusion constant D . Spiral waves in MM1 WT model for the tissue diffusion constant (a) $D \times 1$, (b) $D \times 2.915$ and that of MM2 WT model for the tissue diffusion constant (c) $D \times 1$ and (d) $D \times 1.299$.

CV by $\simeq 8.2\%$. The changes in CV are consistent with those mentioned in Ref. [53].

APPENDIX C: SPIRAL-WAVE DYNAMICS IN MM1 WT AND MM2 WT MODELS WITH BOTH VALUES OF THE DIFFUSION CONSTANT D

As we have mentioned in Sec. III of the main paper, the conduction-velocity (CV) of MM1 WT and MM2 WT lies below the physiological range of CV (see, e.g., Ref. [18]). Therefore, in some representative simulations, we have increased CV for these two models (roughly $CV \propto \sqrt{D}$). The changed values of D for MM1 WT and MM2 WT are $D \times 2.915$ and $D \times 1.299$, respectively. Figure 13 compares the spiral waves with these changed and unchanged values of D . Note that, apart from the change in ω and CV and an increase in the arm length, the qualitative dynamics of these spiral waves remains the same.

APPENDIX D: CONTROL OF SPIRAL WAVES

The development of control strategies for the elimination of spiral- and scroll-wave turbulence is of paramount importance in searching for low-amplitude defibrillation schemes. One such scheme, which has been especially successful in the elimination of spiral-wave turbulence in a variety of mathematical models for cardiac tissue [3,4,21,54–56], eliminates spiral waves by electrical stimulation on a square mesh. We investigate the efficacy of such a control scheme in the TP06, MM1 WT, MM2 WT, MM1 MUT, and MM2 MUT models. In our illustrative study, the simulation domain is divided into square cells of dimension 128×128 grid points (for a domain of size 1024×1024) and 64×64 grid points (for a domain of size 512×512); and then we apply a stimulus, of amplitude 50 pA/pF , for 100 ms along the edges of the square cells, as in

FIG. 14. Pseudocolor plots of the transmembrane potential V_m illustrating the elimination of spiral waves by electrical stimulation on a square mesh. The domain is divided into square cells of dimension 128×128 grid points (for a domain size 1024×1024) or 64×64 (for a domain size 512×512); and then a stimulus, of amplitude 50 pA/pF, is applied for 100 ms along the edges of the square cells as in Ref. [54]; this leads to the elimination of spiral-wave activity in all the models we study. For the spatiotemporal evolution of spiral waves see movie M11 in Ref. [17].

Ref. [54]; this leads to the elimination of spiral-wave activity in both MM1 MUT and MM2 MUT, this scheme also works for all the other models (TP06, MM1 WT, and MM2 WT) that we have studied as we show in Fig. 14 (for the spatiotemporal evolution of spiral waves, see movie M11).

APPENDIX E: PARAMETER-SENSITIVITY ANALYSIS

We carry out a detailed parameter-sensitivity study principally for the WT models by using multivariable linear regression; in particular, we use partial least square (PLS) analysis (see, e.g., Ref. [57]). We have restricted our analysis only to the maximal conductances ($G_{i,\max}$ for channel (i) and the maximal fluxes $K_{i,\max}$ of pumps and exchangers. To perform this PLS, we require (a) input data (the independent variables such as $G_{\text{Na},\max}$), called *predictors*, and (b) the corresponding output data (the dependent variables, e.g., APD), called *responses*. To obtain cellular responses, we consider 500 samples of our input data set, namely, the scaled values of maximal conductances and fluxes of the pumps, ion channels, and ion exchangers; we get the positive, but random, scaling factors from a log-normal distribution with a given standard deviation σ . The 12 predictors that we consider, at the cellular level, are

$$X_{\text{cell}} = \{G_{\text{Na}}, G_{\text{CaL}}, G_{\text{to}}, G_{\text{Ks}}, G_{\text{Kr}}, G_{\text{K1}}, K_{\text{NaCa}}, P_{\text{NaK}}, G_{\text{pCa}}, G_{\text{pK}}, G_{\text{bNa}}, G_{\text{bCa}}\} \quad (\text{E1})$$

and we measure the three responses

$$Y_{\text{cell}} = \{V_{\max}, \text{APD}, V_{\text{rest}}\}. \quad (\text{E2})$$

We pace the cell with $PCL = 1000$ ms for 100 pulses; and we then record the predictor and response data sets for 500 samples, each with a different random scaling factor. We mean-center the predictor and response data sets, and we normalize them such that the standard deviation is unity as in Ref. [57].

Likewise, in our tissue-level studies, we consider 500 samples of the input data set with the 12 predictors as in Eq. (E1) and the two responses

$$Y_{\text{tissue}} = \{\text{APD}, \text{CV}\}. \quad (\text{E3})$$

We pace our tissue with $PCL = 1000$ ms for 20 pulses, record the predictor and response data sets, mean-center them, and then normalize them so that the standard deviation is unity.

To assess, the differences observed in AP morphology because of different models for Na ion-channel, we carry out a detailed parameter-sensitivity study principally for the WT models by using multivariable linear regression. The models we consider contain $\simeq 20$ – 30 parameters or predictors [see, e.g., Eq. (E1)]. The responses [see, e.g., Eqs. (E2) and (E3)] change if we change these predictors. To assess the extent of these changes, we carry out a parameter-sensitivity study that is especially useful when we compare the results of different models. In particular, we perform the PLS multivariable-linear-regression analysis. We choose the random numbers (for scaling the conductances and fluxes) from the log-normal distribution shown in Fig. 15(a); in this way, we get 500 sets of conductances and fluxes (predictors); with each one of these sets we obtain the corresponding sets of responses. We display two representative histograms for the predictors in Figs. 15(b)

FIG. 15. Results of PLS regression analysis. (a) Plot of the log-normal distribution from which we obtain random numbers for scaling the predictors. [(b) and (c)] Shows this histograms of G_{Na} and G_{CaL} respectively, that we obtain from 500 samples.

and 15(c), for $\sigma = 0.25$. We use 400 of these sets for the PLS regression analysis (see Ref. [58]) to obtain the regression matrix B_{pls} [Eq. (E6)]; note that, in the cellular (tissue) case, this is a 12×3 (12×2) matrix, whose rows and columns are labeled, respectively, by the predictors and responses. We

use B_{pls} to predict the responses for the remaining 100 sets of conductances and fluxes. We then compare these predicted values of the responses with those from our direct simulations for these 100 sets; this comparison yields the goodness-of-fit parameter R^2 (see Eq. (E7) and the plots in Fig. 16).

FIG. 16. The actual versus predicted plots for all the 3 responses (V_{max} , APD and V_{rest}) at the cellular level and one response (CV) at the tissue level for 12 predictors for all the three wild-type models. Row (a) shows these results in TP06 model, row (b) shows that in MM1 WT model and row (c) shows that in MM2 WT model. 100 data sets were considered for testing the PLS regression models. R^2 values inside the plots show the goodness of the model.

FIG. 17. Sensitivity studies of the responses such as $V_{\max}$, APD, V_{rest} and CV, for the WT models. The predictors are G_{Na} , G_{CaL} , G_{to} , G_{Ks} , G_{Kr} , G_{K1} , K_{NaCa} , P_{NaK} , G_{pCa} , G_{pK} , G_{bNa} , and G_{bCa} . These predictors are varied using random numbers picked from log-normal distribution of width $\sigma = 0.25$.

Partial least squares (PLS) regression algorithm.

(1) We perform a principal component analysis (PCA) (see Ref. [59]) for the predictors X [Eq. (E1)] and the responses Y [Eqs. (E2) and (E3)] to obtain (a) the scores T and the loadings P of X and (b) the scores U and loadings Q of Y (see, e.g., Ref. [59]).

$$X = \mathcal{T}P^T; \quad Y = UQ^T; \quad (\text{E4})$$

here, X , P , and Q are vectors, $\mathcal{T}$ is a matrix, and the superscript T denotes a transpose.

(2) By correlating the scores of Y , i.e., U with respect to the scores of X , i.e., $\mathcal{T}$ we get

$$Y = \mathcal{T}BQ^T, \quad (\text{E5})$$

where B is a matrix.

(3) The regression matrix is given by

$$B_{\text{pls}} = PBQ^T. \quad (\text{E6})$$

(4) The goodness of fit is

$$R^2 = 1 - \frac{SS_{\text{residual}}}{SS_{\text{total}}}, \quad (\text{E7})$$

where

$$SS_{\text{residual}} = \sum_i (Y_{i,\text{simulated}} - Y_{i,\text{predicted}})^2$$

and

$$SS_{\text{total}} = \sum_i (Y_{i,\text{simulated}} - \bar{Y}_{\text{simulated}})^2.$$

We look at the sensitivity of the four responses, namely, $V_{\max}$, APD, and V_{rest} , at the cellular level, and one response, CV, at the tissue level, with respect to the twelve predictors shown in Fig. 17 for all the WT models. The vertical axis in the plot, for a given response j [e.g., $j = V_{\max}$, APD, V_{rest} , and CV in Figs. 17(a)–17(d)], is $B_{\text{pls}}(i, j)$; the horizontal axis lists the predictors i . Figs. 17(a)–17(c) are plots for the cellular case; Fig. 17(d) is a plot for the tissue

FIG. 18. Plots of some predictors vs some responses comparing simulated (blue) and predicted (red) values: (a) $V_{\max}$ vs G_{Na} ; (b) APD vs G_{CaL} ; (c) APD vs G_{Kr} ; (d) CV vs G_{Na} in our 2D tissue studies. The values of R^2 indicate the goodness of the fit.

study. In these plots, positive (negative) values of $B_{pls}(i, j)$ imply that an increase in the value of the predictor i increases (decreases) the value of the response j . For example, $B_{pls}(G_{Na}, V_{\max}) = 0.86$ in the TP06 model, which means that an increase in G_{Na} by 20% increases the $V_{\max}$ by $\simeq 17\%$ (this follows [57] because $B_{pls} \times \Delta G_{Na} = 0.86 \times 0.20 = 0.172\%$ which is $\simeq 17\%$); $B_{pls}(G_{Ks}, APD) = -0.62$, in the TP06 model, so an increase in G_{Ks} by 30% decreases APD by $\simeq 18\%$. Therefore the plots in Figs. 17(a)–17(d) give us a synoptic view of the sensitivity of the responses in the TP06, MM1 WT, and MM2 WT models to the predictors that we have considered for the purposes of illustration. Figure 16 show plots that yield R^2 , the goodness-of-fit, for these models. We do not give the plots for the MM1 MUT and MM2 MUT models because $R^2 \simeq 80\%$ and $\simeq 0.01\%$ for these models, respectively. We have also tested the regression models by varying a single predictor while keeping other predictors at the control values. The principle qualitative results of our parameter-sensitivity analysis are as follows.

(1) $V_{\max}$ is mainly controlled by the predictor G_{Na} , which is the case for all the models we study (Fig. 17). In case of the MM2 WT model, G_{CaL} contributes to an increase in $V_{\max}$, but G_{CaL} decreases $V_{\max}$ in the TP06 and MM1 WT models.

(2) The APD is mainly controlled by the predictors G_{CaL} , G_{Kr} , and G_{Ks} . There is a small positive contribution from G_{Na} to the APD in the MM2 WT model, because of the late Na current.

In Fig. 18, we show plots of (a) G_{Na} versus $V_{\max}$, (b) G_{CaL} versus APD, (c) G_{Ks} versus APD, and (d) G_{Na} versus CV for the TP06 model; blue and red curves show, respectively, direct-simulation and predicted values; the latter are linear by

TABLE IV. The table compares the 2D and 3D simulation run-times of all the models used in our study whose simulations are performed in machine 2.

Models	2D	3D
	size = 1024×1024 for $T_{\text{sim}} = 10$ s (in hours)	size = $1024 \times 1024 \times 40$ for $T_{\text{sim}} = 2$ s (in hours)
TP06	4.86	12.55
MM1 WT	9.03	19.27
MM2 WT	15.64	28.21
MM1 MUT	9.29	21.36
MM2 MUT	20.61	63.38

the very nature of our regression analysis; the former show some nonlinearity, especially in the plots (a), (b), and (d).

APPENDIX F: COMPARISON OF COMPUTATIONAL COST OF ALL THE MODELS

We have used the following two machines for our 2D and 3D computations. (1) Machine 1: *AMD Opteron(tm) Processor 6376* CPU model with each processor operating at 2.3 GHz. (2) Machine 2: *Intel(R) Xeon(R) CPU E5-2670 0* CPU model with each processor operating at 2.6 GHz.

For the comparison purpose, we provide the runtimes of all the models whose simulations are performed in machine 2. The Table IV provides an overview of the computational costs for the 2D and the 3D simulations and the number of processors used are 64 and 256 for 2D and 3D simulations, respectively. We can observe that, indeed, the computational costs of simulating MM models are higher than those for the TP06 model and furthermore, between the two MM models, the computational cost of the MM2 model is higher compared to the MM1 model.

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