Supplementary Material: Analytical Characterization and Design Guidelines for Membrane Permeation Based on a Four-State Master Equation

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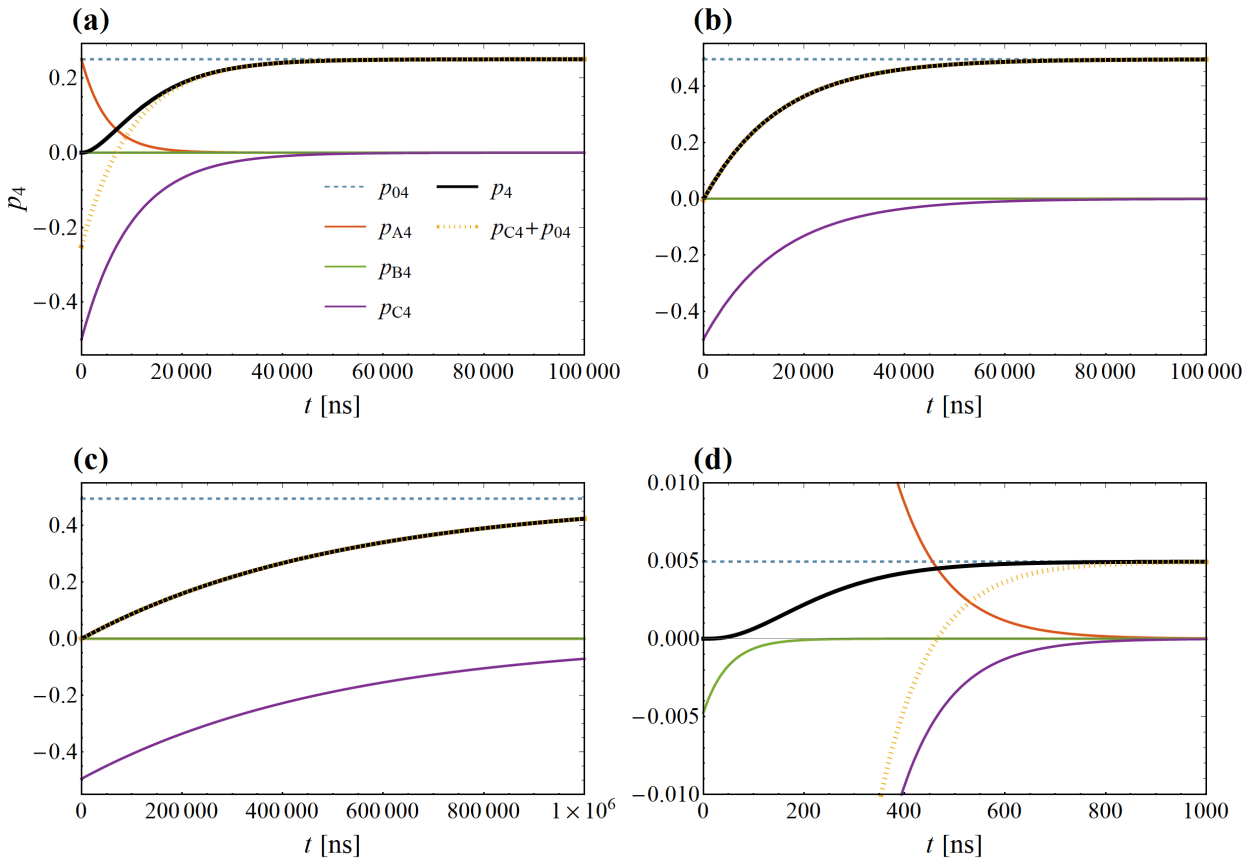


Fig. S1: Time evolutions of the fourth component of the solution, $p_4(t)$, and the fourth components of modes 0, A, B, and C, denoted by $p_{04}(t)$ (mode 0; dashed line), $p_{A4}(t)$ (mode A), $p_{B4}(t)$ (mode B), and $p_{C4}(t)$ (mode C), for the initial condition $\mathbf{p}(0) = (1, 0, 0, 0)^T$. The sum $p_{C4}(t) + p_{04}(t)$ is shown by a dotted line. The rate parameters are (a) $k_{in} = k_{out} = 0.0001\,\mathrm{ns}^{-1}$ and $k_{tra} = 0.01\,\mathrm{ns}^{-1}$, (b) $k_{in} = 0.0001\,\mathrm{ns}^{-1}$ and $k_{out} = k_{tra} = 0.01\,\mathrm{ns}^{-1}$, (c) $k_{in} = k_{tra} = 0.0001\,\mathrm{ns}^{-1}$ and $k_{out} = 0.01\,\mathrm{ns}^{-1}$, and (d) $k_{in} = k_{tra} = 0.01\,\mathrm{ns}^{-1}$ and $k_{out} = 0.0001\,\mathrm{ns}^{-1}$.

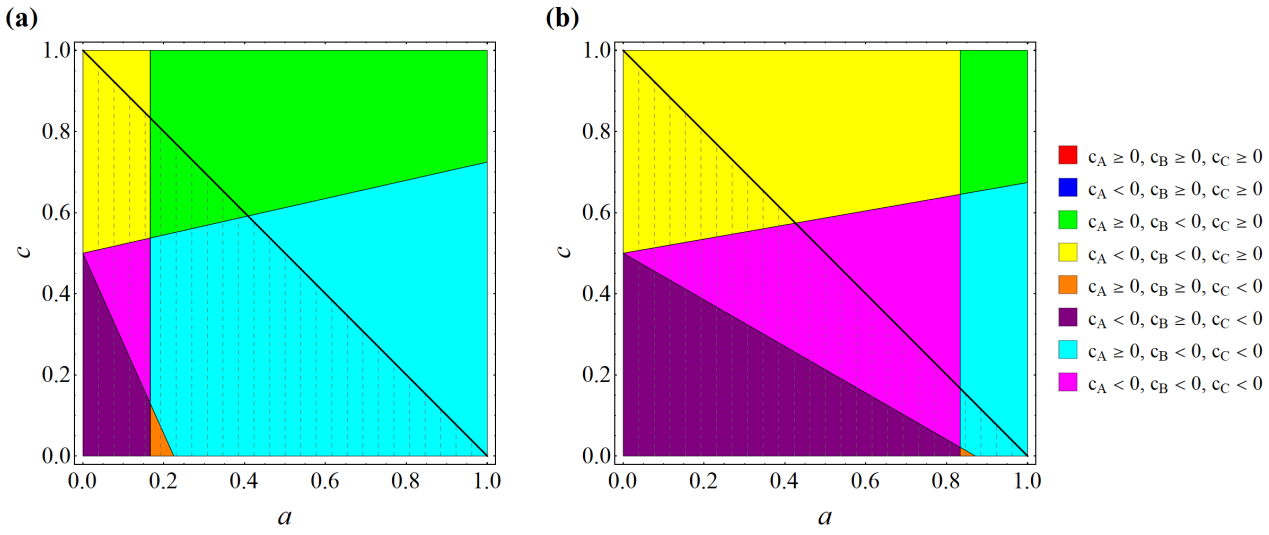


Fig. S2: (a) Sign patterns of c_A, c_B, and c_C for $k_{in} = 5k$ and $k_{tra} = k_{out} = k$. Unlike the uniform-rate case shown in Fig. 3 in the main text, sign pattern (iii), $c_A \geq 0$, $c_B < 0$, and $c_C \geq 0$, occurs within the target triangular region Ω depicted by dashed lines. (b) Sign patterns of $k_{in} = k_{tra} = k, k_{out} = 5k$.

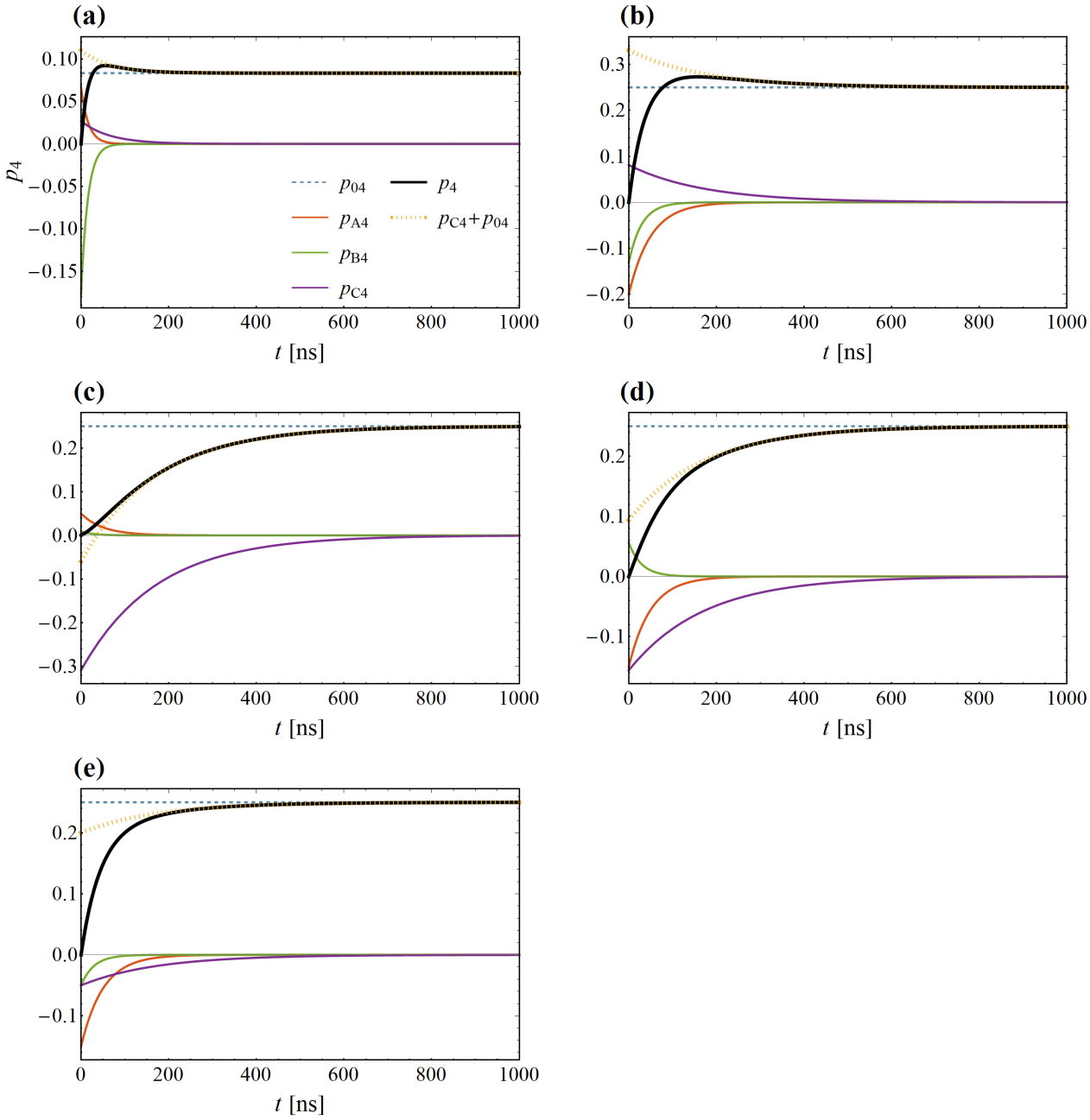


Fig. S3: Time evolutions of the fourth component of the solution, $p_4(t)$, and the fourth components of modes 0, A, B, and C, denoted by $p_{04}(t)$ (dashed line), $p_{A4}(t)$, $p_{B4}(t)$, and $p_{C4}(t)$, respectively, for the initial condition $\mathbf{p}(0) = (a, b, c, 0)^T$. The sum $p_{C4}(t) + p_{04}(t)$ is shown by a dotted line. (a) Case (iii), with $a = 0.3$, $b = 0$, $c = 0.7$, and $k_{\text{in}} = 0.05\,\text{ns}^{-1}$ and $k_{\text{out}} = k_{\text{tra}} = 0.01\,\text{ns}^{-1}$; (b) case (iv), with $a = b = 0.1$, $c = 0.8$ and $k_{\text{in}} = k_{\text{out}} = k_{\text{tra}} = 0.01\,\text{ns}^{-1}$; (c) case (v), with $a = 0.6$, $b = 0.35$, $c = 0.05$ and the same uniform rate

parameters; (d) case (vi), with $a = c = 0.2$, $b = 0.6$ and the same uniform rate parameters; and (e) case (viii), with $a = 0.2$, $b = 0.3$, $c = 0.5$ and the same uniform rate parameters. Here, cases (iii), (iv), (v), (vi), and (viii) refer to the sign patterns defined in Table I of the main text. The nonuniform rate parameters are used only in panel (a), because case (iii) is not realized with the uniform rate parameters, as shown in Fig. 3 of the main text. With the rate parameters used in panel (a), case (iii) occurs, as shown in Fig. S2(a).

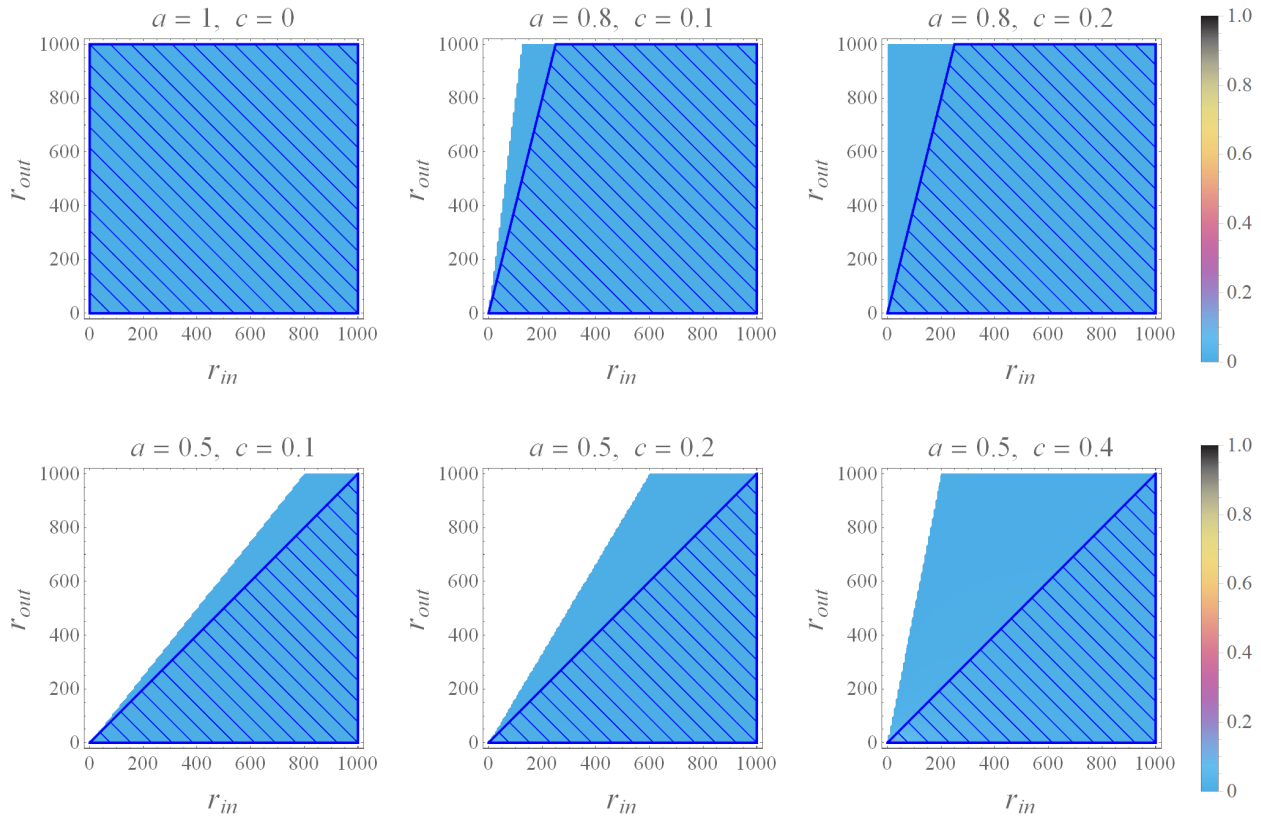


Fig. S4: The $(r_{\rm in}, r_{\rm out})$ region shown in Fig. 4 of the main text is displayed over a wider range. R_∞ tends to decrease as $r_{\rm in}$ or $r_{\rm out}$ increases. The exceptional region shown in Fig. 4 is not discernible here because of the broader range displayed.

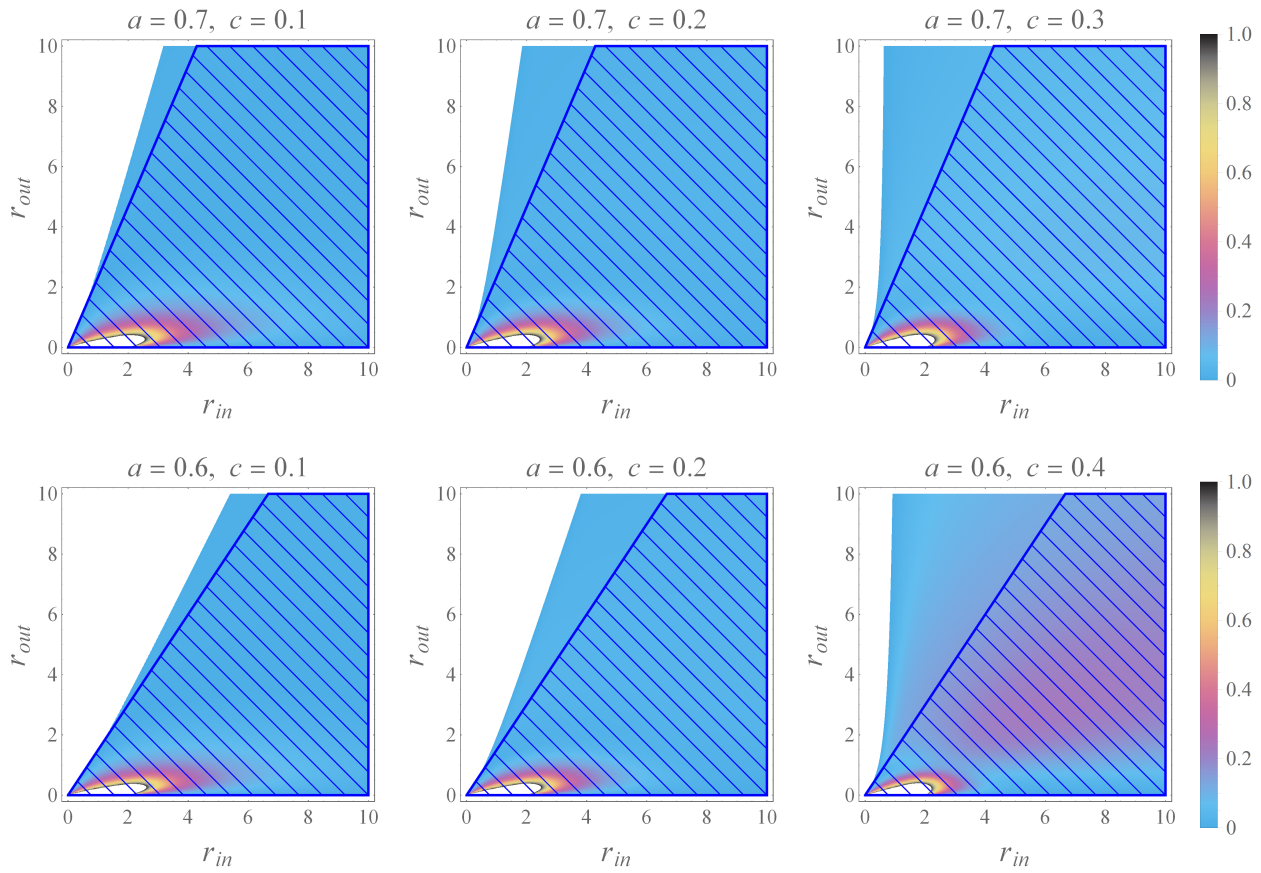


Fig. S5: Plots for $a = 0.7$ and 0.6, with c varying over $0 \leq c \leq 1 - a$, constructed in the same manner as Fig. 4 in the main text.

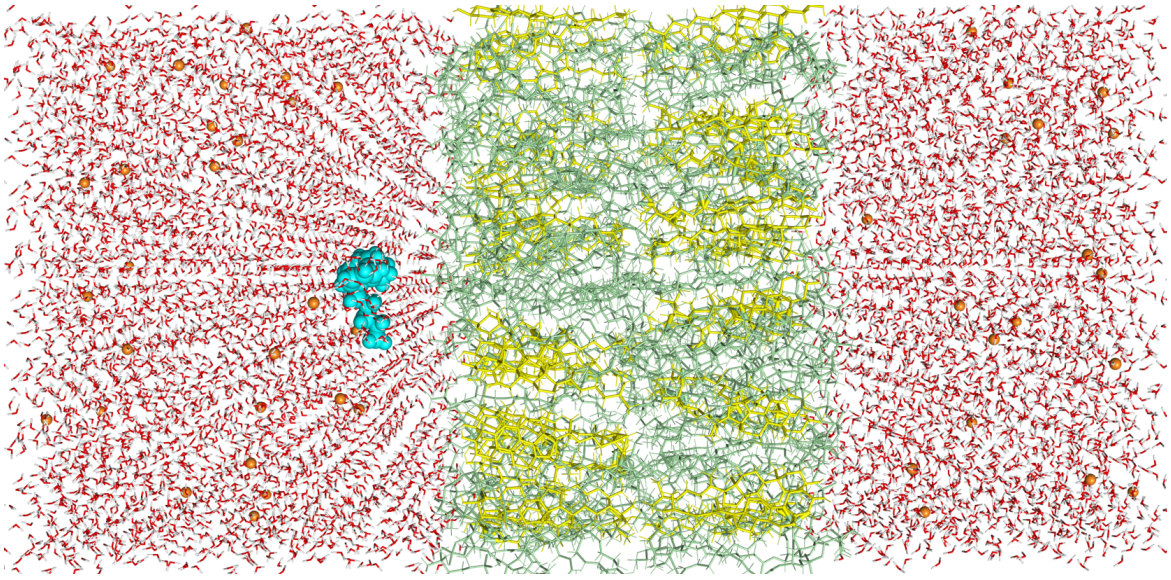


Fig. S6: Snapshot of all molecules in the MD simulation box. The membrane system consisted of 72 POPC molecules (green) and 48 cholesterol molecules (yellow), and the surrounding environment contained TIP3P water molecules and ions. Desipramine molecule (cyan) is in the water of site 1.

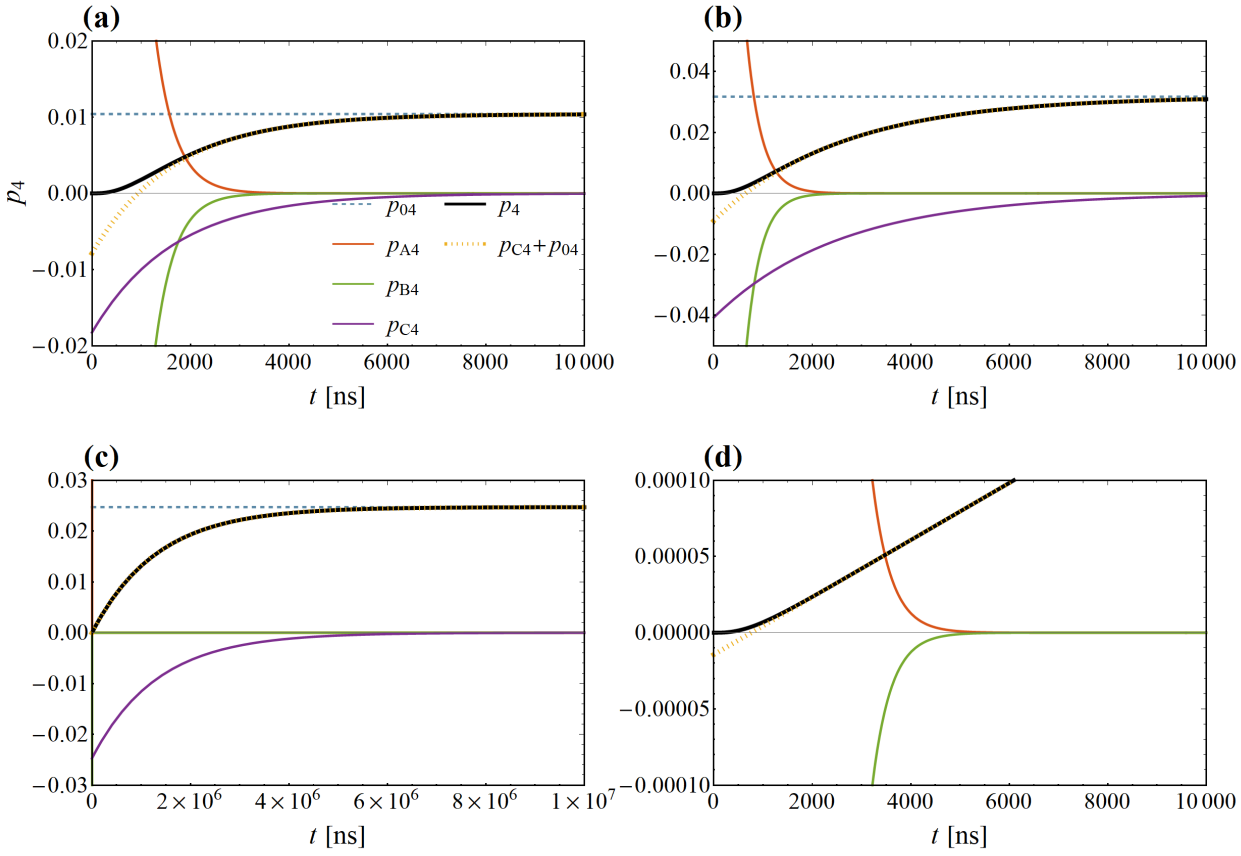


Fig. S7: Panels (a)–(c) show the time evolution of the fourth component of the solution, $p_4(t)$, and the fourth components of modes 0, A, B, and C, denoted by $p_{04}(t)$ (dashed line), $p_{A4}(t)$, $p_{B4}(t)$, and $p_{C4}(t)$, respectively, together with the combined contribution of modes C and 0, $p_{C4}(t)+p_{04}(t)$ (dotted line), for (a) Loperamide, (b) Labetalol, and (c) Domperidone. The initial condition is $\mathbf{p}(0) = (1, 0, 0, 0)^T$, and the rate parameters are given in Table III in the main text. Panel (d) is an enlargement of panel (c).

The results for these three molecules, together with those for Desipramine shown in Fig. 9 in the main text, exhibit a tendency for modes A and B to cancel each other. For the specified initial condition, the expansion coefficients of modes A and B have opposite signs ($c_A < 0$ and $c_B > 0$), as do those of modes C and 0 ($c_C < 0$ and $q_\infty > 0$). Moreover, the initial contributions of the two mode groups have equal absolute values:

$$|c_A + c_B| = |c_C + q_\infty|.$$

This relation follows from $0 = p_4(0) = c_A + c_B + c_C + q_\infty$. Thus, the two groups, modes C and 0 and modes A and B, start with contributions of equal absolute magnitude but opposite

signs. As shown in the figures, these contributions are small at $t = 0$, with magnitudes of approximately 0.01 or less (about 10^{-5} for Domperidone). In this sense, the combined contribution of modes A and B counterbalances that of modes C and 0 at the initial time.

For all four molecules, every initial condition satisfying condition (40), namely $a \geq a_{\min} = 0.5$ in these $r_{in} \geq r_{out}$ cases, belongs to case (vii) for the sign pattern of the coefficients (see Fig. S10). Therefore, the observed cancellation between modes A and B is not strongly dependent on the choice of initial condition within this range.

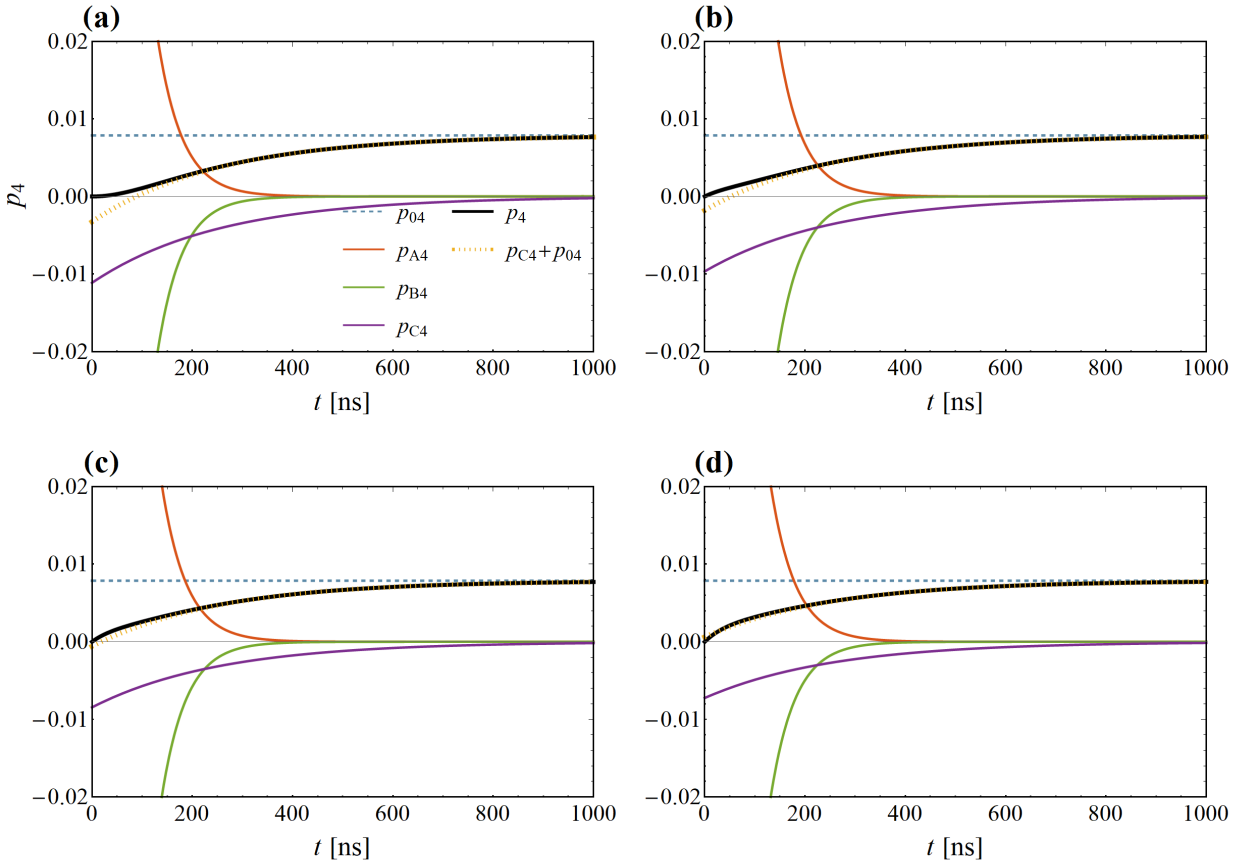


Fig. S8: Time evolution of the fourth component of the solution, $p_4(t)$, and the fourth components of modes 0, A, B, and C, denoted by $p_{04}(t)$ (dashed line), $p_{A4}(t)$, $p_{B4}(t)$, and $p_{C4}(t)$, respectively, together with the combined contribution of modes C and 0, $p_{C4}(t) + p_{04}(t)$ (dotted line), for Desipramine. The rate parameters are given in Table III in the main text. The initial conditions $\mathbf{p}(0) = (a, b, c, 0)^T$ are set to (a) $a = 0.6$, $b = 0.4$, $c = 0$, (b) $a = 0.8$, $b = c = 0.1$, (c) $a = 0.7$, $b = c = 0.15$, and (d) $a = 0.6$, $b = c = 0.2$.

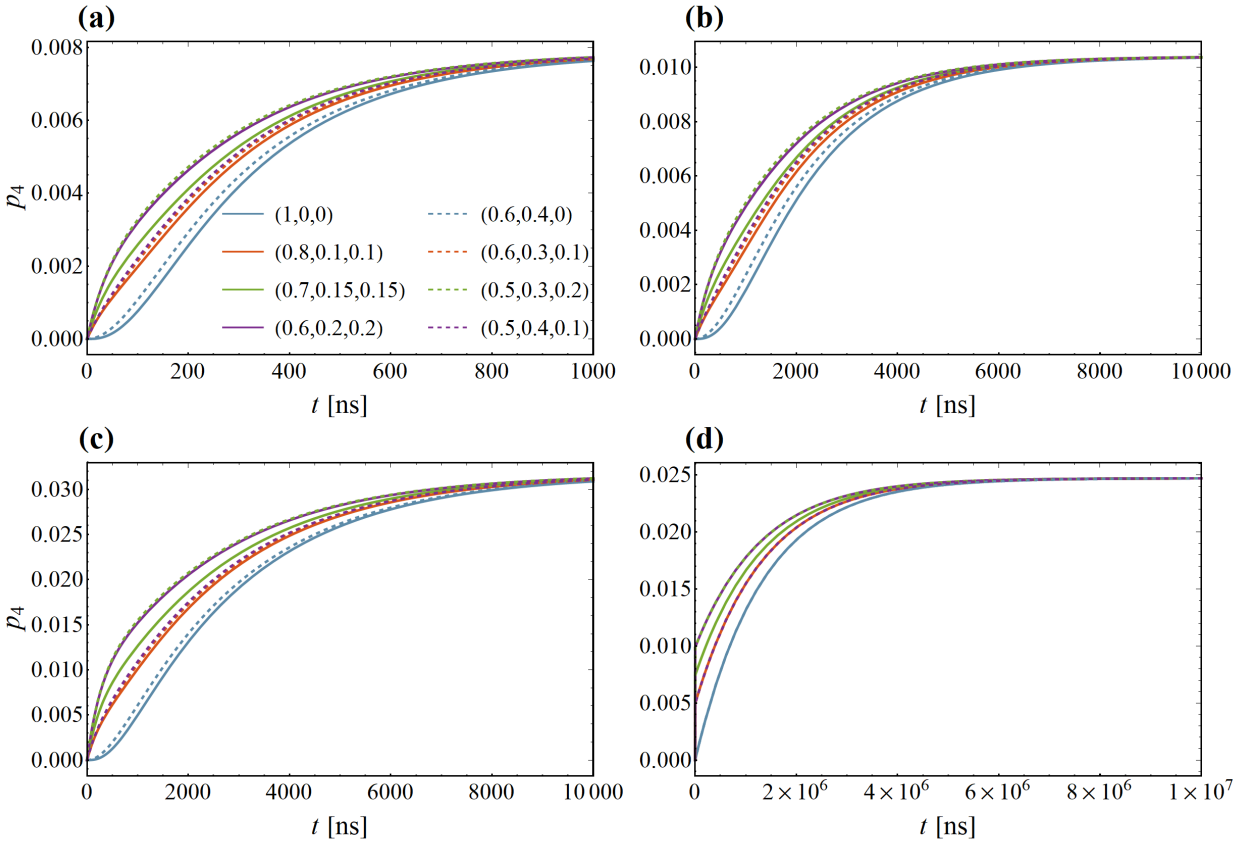


Fig. S9: Time evolution of the fourth component of the solution, $p_4(t)$, for (a) Desipramine, (b) Loperamide, (c) Labetalol, and (d) Domperidone. The rate parameters are given in Table III in the main text. The initial conditions $\mathbf{p}(0) = (a, b, c, 0)^T$ are set to $(a, b, c) = (1, 0, 0)$, $(0.8, 0.1, 0.1)$, $(0.7, 0.15, 0.15)$, $(0.6, 0.2, 0.2)$ for solid lines, and $(a, b, c) = (0.6, 0.4, 0)$, $(0.6, 0.3, 0.1)$, $(0.5, 0.3, 0.2)$, and $(0.5, 0.4, 0.1)$ for dashed lines.

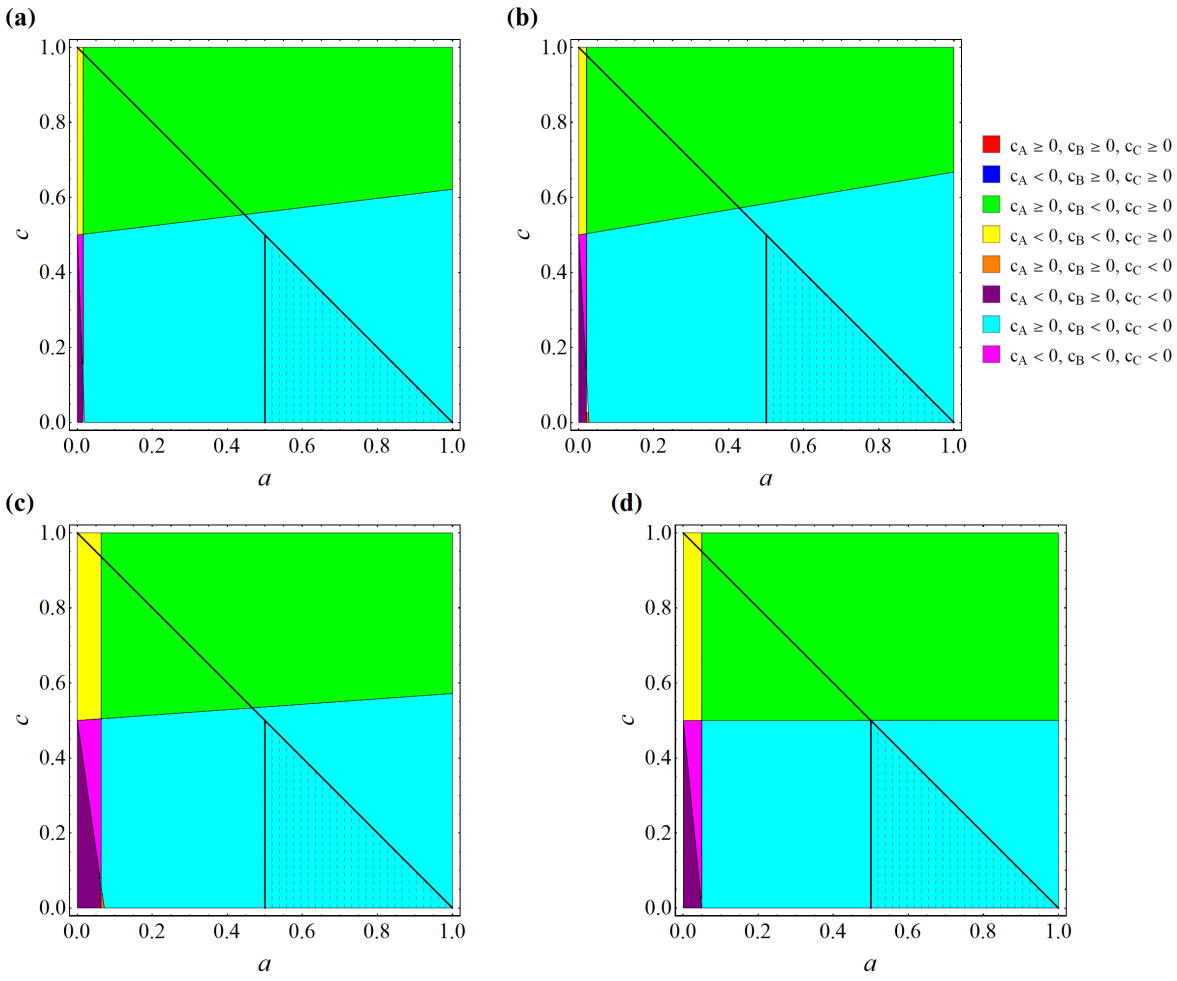


Fig. S10: Sign patterns of c_A, c_B, and c_C for (a) Desipramine, (b) Loperamide, (c) Labetalol, and (d) Domperidone. The rate parameters are given in Table III in the main text. The dashed lines indicate the points (a, c) satisfying condition $a \geq a_{\min} = 0.5$ in Ω.