situation with high collision efficiencies (diffusion controlled association), higher levels of R will reduce association rates in general due to slower protein mobility, but this trend is weak for static organized R configurations.

Supporting Information. Simulations varying the number of active sites. Simulations of the tracks configuration varying the track mean length.

ACKNOWLEDGMENTS. We would like to thank Juan Manuel Pedraza for the motivation he provided at the initial stages of this work. This work was supported with funding from the Faculty of Sciences at Universidad de los Andes.

REFERENCES

(1) Rieke, F.; Baylor, D.A. Single-photon detection by rod cells of the retina. Rev. Mod. Phys. 1998, 70, 1027-1036.

(2) Cone, R.A. Rotational diffusion of rhodopsin in the visual receptor membrane. Nat. New Biol. 1972, 236, 39-43.

(3) Poo, M.M.; Cone, R.A. Lateral diffusion of rhodopsin in the photoreceptor membrane. Nature. 1974, 247, 438-441.

(4) Whited, A.M.; Park, P.S.H. Nanodomain organization of rhodopsin in native human and murine rod outer segment disc membranes. Biochim. Biophys. Acta - Biomembr. 2015, 1848, 26-34.

(5) Liang, Y.; Fotiadis, D.; Filipek, S.; Saperstein, D.A.; Palczewski, K.; Engel, A. Organization of the G protein-coupled receptors rhodopsin and opsin in native membranes. J. Biol. Chem. 2003, 278, 21655-21662.

(6) Suda, K; Filipek, S.; Palczewski, K.; Engel, A.; Fotiadis, D. The supramolecular structure of the GPCR rhodopsin in solution and native disc membranes. Mol. Membr. Biol. 2004, 21, 435-446.

(7) Palczewski, K. Oligomeric forms of G protein-coupled receptors (GPCRs). Trends Biochem. Sci. 2010;35:595-600.

(8) Fotiadis, D.; Liang, Y.; Filipek, S.; Saperstein, D.A.; Engel, A.; Palczewski, K. Atomic-Force microscopy: Rhodopsin dimers in native disc membranes. Nature. 2003, 421, 127-128.

(9) Buzhynskyy, N.; Salesse, C.; Scheuring, S. Rhodopsin is spatially heterogeneously distributed in rod outer segment disk membranes. J. Mol. Recognit. 2011, 24, 483-489.

(10) Gunkel, M.; Schöneberg, J.; Alkhaldi, W.; Irsen, S.; Noé, F; Kaupp, U.B; Al-Amoudi, A. Higher-order architecture of rhodopsin in intact photoreceptors and its implication for phototransduction kinetics. Structure. 2015, 23, 628-638.

(11) Govardovskii, V.I.; Korenyak, D.A.; Shukolyukov, S.A.; Zueva, L.V. Lateral diffusion of rhodopsin in photoreceptor membrane: a reappraisal. Mol. Vis. 2009, 15, 1717-1729.

(12) Govardovskii, V.I.; Firsov, M.L. Unknown mechanisms regulating the GPCR signal cascade in vertebrate photoreceptors. Neurosci. Behav. Physiol. 2012, 42, 180-192.

(13) Dell'Orco, D. A physiological role for the supramolecular organization of rhodopsin and transducin in rod photoreceptors. FEBS Lett. 2013, 587, 2060-2066.

(14) Dell'Orco, D.; Schmidt, H. Mesoscopic Monte Carlo simulations of stochastic encounters between photoactivated rhodopsin and transducin in disc membranes. J. Phys. Chem. B. 2008, 112, 4419-4426.

(15) Schöneberg, J.; Heck, M.; Hofmann, K.P.; Noé, F. Explicit spatiotemporal simulation of receptor-G protein coupling in rod cell disk membranes. Biophys. J. 2014, 107, 1042-1053.

(16) Kim, J.S.; Yethiraj, A. Effect of macromolecular crowding on reaction rates: A computational and theoretical study. Biophys. J. 2009, 96, 1333-1340.

(17) Kim, J.S.; Yethiraj, A. Crowding effects on association reactions at membranes. Biophys. J. 2010, 98, 951-958.

(18) Palczewski, K. G protein–coupled receptor rhodopsin. Annu. Rev. Biochem. 2006, 75, 743-

767.

(19) Lambright, D.G.; Sondek, J.; Bohm, A.; Skiba, N.P.; Hamm, H.E.; Sigler, P.B. The 2.0 Å crystal structure of a heterotrimeric G protein. Nature. 1996, 379, 311-319.

(20) Filipek, S.; Krzysko, K.A.; Fotiadis, D; Liang, Y.; Saperstein, D.A.; Engel, A.; Palczewski, K. A concept for G protein activation by G protein-coupled receptor dimers: The transducin/rhodopsin interface. Photochem. Photobiol. Sci. 2004, 3, 628-638.

(21) Wang, Q.; Zhang, X.; Zhang, L.; He, F.; Zhang, G.; Jamrich, M.; Wensel, T. Activation-dependent hindrance of photoreceptor G protein diffusion by lipid microdomains. J. Biol. Chem. 2008, 283, 30015-30024.

(22) Buján-Nuñez, M.C.; Miguel-Fernández, A.; López-Quintela, M.A. Diffusion-influenced controlled reaction in an inhomogeneous medium: Small concentration of reagents. J. Chem. Phys. 2000, 112, 8495-8501.

(23) Saxton, M.J. Anomalous diffusion due to obstacles: a Monte Carlo study. Biophys. J. 1994;66:394-401.

(24) Dell'Orco, D.; Koch, K.W. A dynamic scaffolding mechanism for rhodopsin and transducin interaction in vertebrate vision. Biochem J. 2011;440:263-271.

(25) Fanelli, F.; Dell'Orco, D. Rhodopsin activation follows precoupling with transducin: Inferences from computational analysis. Biochemistry. 2005, 44, 14695-14700.

(26) Kahlert, M.; Hofmann, K.P. Reaction rate and collisional efficiency of the rhodopsin-transducin system in intact retinal rods. Biophys, J. 1991;59:375-386.

(27) Cangiano, L.; Dell'Orco, D. Detecting single photons: A supramolecular matter? FEBS Lett. 2013, 587, 1-4.

(28) Yau, K.W.; Hardie, R.C. Phototransduction motifs and variations. Cell. 2009, 139, 246-264.

(29) Lopez-Gimenez, J.F.; Canals, M.; Pediani, J.D.; Milligan, G. The alpha1b-Adrenoceptor Exists as a Higher-Order Oligomer: Effective oligomerization is required for receptor

maturation, surface delivery, and function. Mol. Pharmacol. 2007, 71, 1015-1029.

(30) Liste, M.J.V.; Caltabiano, G.; Ward, R.J.; Alvarez-Curto, E.; Marsango, S.; Milligan, G. The molecular basis of oligomeric organization of the human M3 muscarinic acetylcholine receptor. Mol. Pharmacol. 2015, 87, 936-953.

(31) Ward, R.J.; Pediani, J.D.; Godin, A.G.; Milligan, G. Regulation of oligomeric organization of the serotonin 5-hydroxytryptamine 2C (5-HT2C) receptor observed by spatial intensity distribution analysis. J. Biol. Chem. 2015, 290, 12844-12857.

(32) Armando, S.; Quoyer, J.; Lukashova, V.; Maiga, A.; Percherancier, Y.; Heveker, N.; Pin, J.P.; Prézeau, L.; Bouvier, M. The chemokine CXC4 and CC2 receptors form homo- and heterooligomers that can engage their signaling G-protein effectors and βarrestin. FASEB J. 2014, 28, 4509-4523.

Table of Contents Graphic (TOC)