

Possible mechanisms of auto-phosphorylation of MAPKs using techniques of QM/MM and "Steered MD"

Ramiro G. Rodriguez Limardo^{a,b}, Dardo N. Ferreiro^a, Marcelo A. Marti^a, Adrian G. Turjanski^a.

^a Departamento de Química Biológica/INQUIMAE, Universidad de Buenos Aires, FCEyN, Ciudad Universitaria, Ciudad de Buenos Aires, Argentina

^b (ramiro.grl@qi.fcen.uba.ar)

Mitogen-Activated Protein Kinases (MAPKs) are serin/threonin kinases which phosphorylate proteins with the S/T-P motif^{1,2}. MAPKs require double phosphorylation in two highly conserved tyrosine and threonin residues. In spite of the great knowledge that exists on MAPKs structure, little is known about the mechanism that regulates activation and interaction with other proteins because the static structures are very similar.

In a previous study of the dynamics of one of this proteins, p38 γ ³ (being its phosphorylation site TGY^{4,5}), a new spatial conformation not described before was found. Such conformation has a great stability in which the tyrosine seems to be close to the catalytic site and, as a consequence, it is accessible for its intramolecular auto-phosphorylation.

We want to identify, by the The Jarzynski equality (JE)⁶, the free energy barriers between this structure and the ones already described (where the activation lip is exposed to the solvent) for p38 γ , p38 α and ERK2, in order to compare them with the auto-activation data shown previously experimentally⁷.

In addition, by using a quantum mechanics/molecular mechanics (QM/MM) approach, we use the same mechanism proposed in a previous work⁸ for the phosphoryl transfer, in the conformation in which the tyrosine is close to the catalytic site to see if the tyrosine is able to accept the phosphate,

Our results are in agreement with many experimental results and they will expand our knowledge on this kinases family.

1. Kyriakis, J. M., and Avruch, J., *Physiological Reviews*, 81, 807 – 869 (2001)
2. Widmann, C., Gibson, S., Jarpe, M. B., and Johnson, G. L., *Physiological reviews*, 79, 143 – 180 (1999)
3. Rodriguez Limardo, R. G., Ferreiro, D. N., Roitberg, A. E., Marti, M. A., and Turjanski, A. G., in process
4. Zarubin, T., and Han, J., *Cell Research*, 15, 11-18 (2005)
5. Bellon, S., Fitzgibbon, M. J., Fox, T., Hsiao, H. M., and Wilson, K. P., *Structure*, 7, 1057 – 1065 (1999)
6. Jarzynski C., *Physical Review Letters*, 78, 2690 – 2693 (1997)
7. Emrick, M. A., Lee, T., Starkey, P. J., Mumby, M. C., Resing, K. A., and Ahn, N. G., *PNAS*, 103, 18101 – 18106 (2006)
8. Turjanski, A. G., Hummer, G., and Gutkind, J. S., *J. Am. Chem. Soc.*, 131, 6141 – 6148 (2009)