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# Dimerization Effects in MAPK cascade

The MAPK (Mitogen-Activated Protein Kinase) cascades are among the most important signal transduction pathways in eukaryotic cells. The core of a MAPK pathway comprises a series of sequentially activated kinases, generically referred to as MAP3Ks, MAP2Ks, and MAPKs. Of particular importance are Raf/MEK/ERK and MEKK/MEK/JNK cascades due to their role in stress response, proliferation, differentiation, and the development of cancer. Consequently, these pathways have been extensively modeled. However, the models developed so far ignore homo- and heterodimerization events occurring between kinases within each tier of the cascade. The significance of dimerization of Raf and MEK proteins is especially well documented. In particular, the dimerization of RAF proteins appears critical for their activation - its dysregulation due to mutations or experimental chemotherapeutic inhibitors can lead to oncogenesis [1] or paradoxical activation [2], respectively. The dimerization of MEK1 and MEK2, on the other hand, introduces a novel regulatory mechanism of controlling the pathway's output via feedback phosphorylation by ERK [3]. Lastly, three-member scaffold proteins such as KSR, which assemble signalling complexes, have themselves been shown to dimerize [4], potentially providing a platform for dimerization of other MAPK components. We have incorporated these effects to produce more realistic models of the MAPK cascade as well as to explore their possible role in the pathway's regulation and dynamics.

## References

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