# The ERK-induced Repression of MEK1 and MEK2 in the MAPK Cascade Dynamics

Pawel Z. Kocieniewski[1] and Tomasz Lipniacki[1]

***Short Abstract* — The Raf/MEK/ERK cascade is one of the most studied transduction pathways. However, existing models largely ignore the existence of isoforms of the constituent kinases, and their dimerization. Here, we propose a model of the ERK cascade that includes heretofore neglected differences between isoforms of MEK. Specifically, unlike MEK2, MEK1 is a subject to a negative feedback from ERK. MEK1 was found to confer this feedback to MEK2 via heterodimerization, an interaction of no previously reported functional significance. We incorporated these recently discovered interactions into a mathematical model of the ERK cascade that reproduced the experimental results and allows for predictions on the differences of MEK isoforms activity.**

***Keywords* — MAPK cascade, kinase isoforms, MEK1-MEK2 heterodimer, negative feedback, rule-base modeling.**

## I. Motivation

THE Raf/ERK pathway belongs to the MAPK family and is important in regulating proliferation and differentiation. Its core comprises a cascade of kinases: Raf, Mek, and Erk, all of which have isoforms. As discovered recently there exist regulatory differences between MEK1 and MEK2 isoforms. In particular, MEK1 has unique phosphorylation site (Thr292), which is phosphorylated by ERK, leading to MEK1 and MEK2 accelerated inactivation. Catalanotti et al. 2009 reported that ablation of MEK1 lead to unexpected prolonged activation of ERK and MEK2 in Mouse Embryonic Fibroblasts (MEFs) [1]. They found that the Thr292-dependent negative feedback regulation of MEK1 is transferred to MEK2 due to these isoforms' heterodimerization. We incorporated these interactions to investigate their role and provide a more complete model of the ERK cascade

## II. Model

The model comprises all levels of the cascade from the EGFR membrane receptor to ERK. Upon binding the ligand, EGFR receptors dimerize and undergo phosphorylation. Phosphorylated protomers subsequently bind and activate an adapter protein Sos1. Sos1 then activates Ras, which in turn activates the Raf/MEK/ERK cascade. MEK1 and MEK2 can homo- and heterodimerize. MEK1 can be phosphorylated by ERK at Thr292. We propose that this creates a binding site for the MEK-specific phosphatase, which upon binding dephosphorylates both protomers within the dimer. The model also includes the classical negative feedback to Sos1 from ERK; phosphorylated Sos1 cannot bind the receptor and activate RAS. The model has been implemented using BioNetGen rule-based environment [2], and is defined by 41 rules generating 108 species.

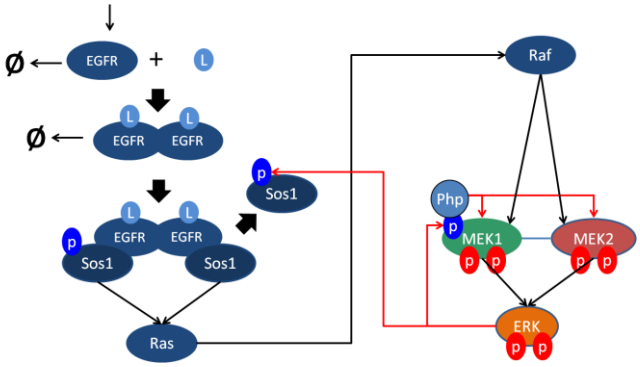


Fig 1. The structure of Raf/MEK/ERK cascade model. The red arrows stand for negative feedback phosphorylations.

## III. Conclusions

The model correctly reproduces the observed profiles of MEK and ERK activation profiles obtained in the experiments with WT and KO MEFs [1]. In particular, the model reproduces prolonged activity of ERK and MEK due to ablation of the negative feedback by (1) MEK1 knockout, (2) mutation of Thr292, and (3) disruption of MEK1/2 heterodimerization. Interestingly, ERK activity profile requires MEK2 to have kinase activity several times greater than MEK1. In summary, MEK isoforms play distinctive roles in the MAPK cascade and their dimerization is functionally important. Furthermore, the isoform specificity and dimerization-dependent cross-regulation was reported for RAF kinases and also deserves investigation.

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[1]Insitute of Fundamental Technological Research, Polish Academy of Science, E-mail: tlipnia@ippt.gov.pl, pkocien@ippt.gov.pl

## References

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[2] Faeder JR, Blinov ML, Hlavacek WS (2009) Rule-based modeling of biochemical systems with BioNetGen.*Methods Mol Biol*. **500**:113-67

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