ATP concentration affects enzymatic processes in time and space

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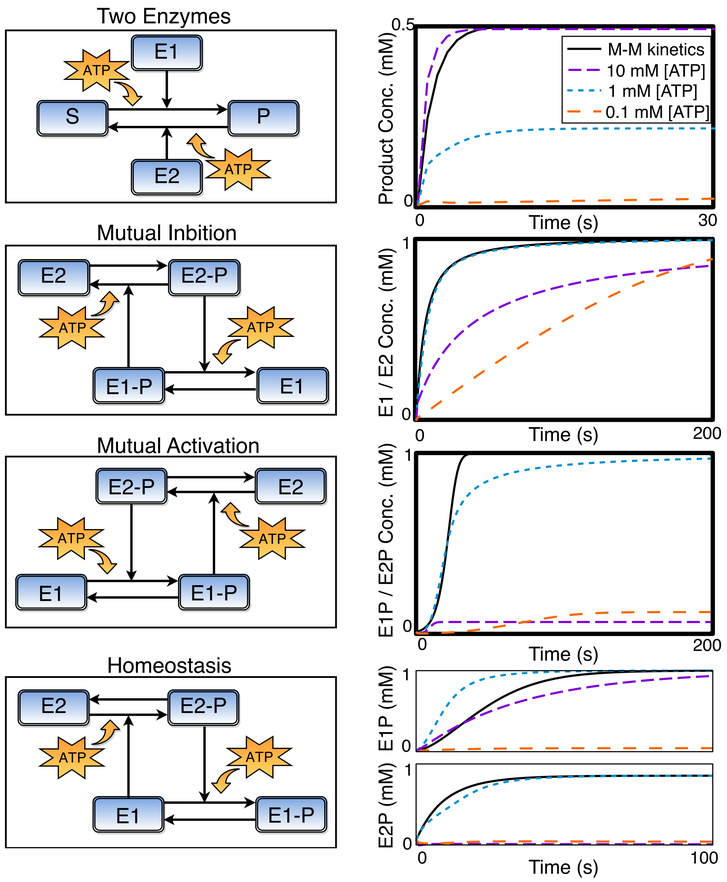
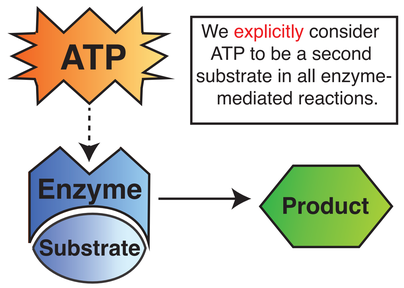
Adenosine 5'-triphosphate (ATP) is the primary "energy currency" of most known living organisms, and thus is a crucial participant in the majority of enzymatic reactions. In standard enzyme kinetics, ATP is assumed to be continually present in large excess, therefore allowing enzyme-mediated processes to be modeled as single-substrate reactions and greatly simplifying the associated mathematical analyses. However, this assumption fails to hold when ATP levels are comparable to substrate levels (e.g., in cellular stress and aging). Here, we demonstrate the importance of ATP concentration on the dynamics of multi-enzyme reactions by explicit consideration of ATP in enzyme-substrate reactions. Our results show that the concentration of ATP plays an important role in determining both the time scale and equilibrium concentrations of the substrate and product.

Effects of ATP on simple two-enzyme modules



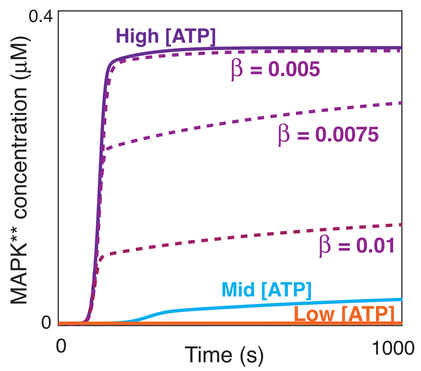


All reactions are modeled as following mass action kinetics.

Characteristics of the MAPK cascade

- Variable duration of response
- Amplification of signal
- Ultrasensitivity to stimulus levels

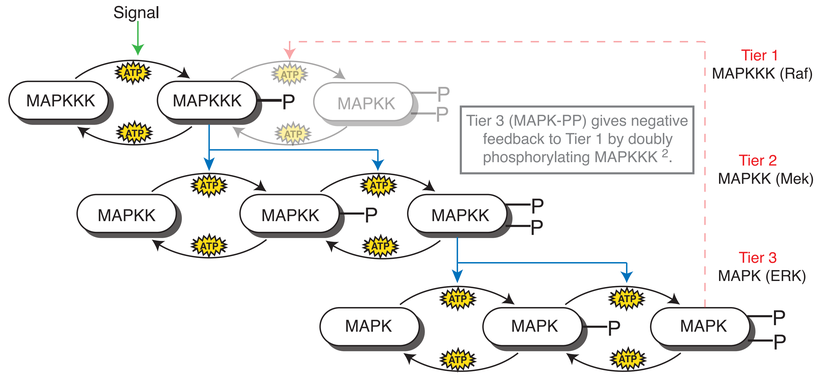
The time course of MAPK activation is significantly affected by ATP levels.



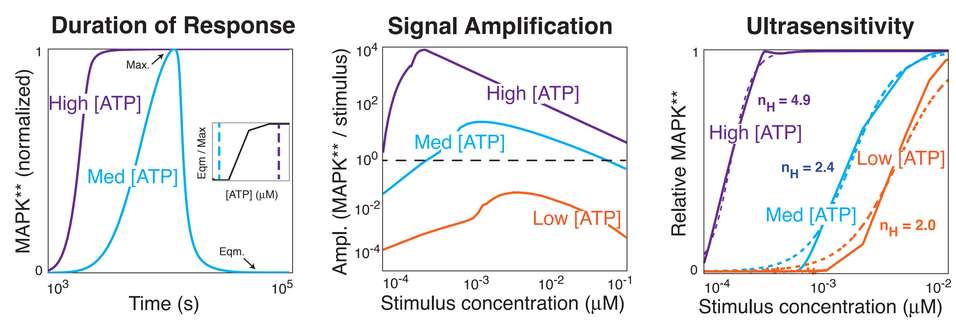
MAPK activation is robust to sudden cellular stress only when initial ATP concentrations are saturating (dashed purple lines). This may not be the case in aging cells, making them more vulnerable to therapeutics.

The MAP kinase cascade

The MAP kinase pathway (or ERK pathway) is a chain of proteins that is involved in communicating almost all cell surface signals to activate a response in the nucleus.

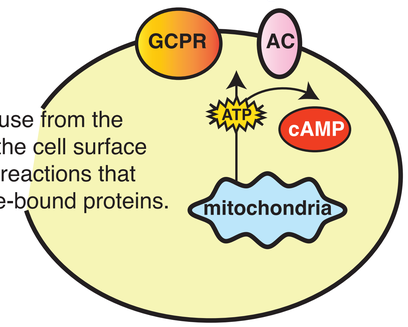


The three-tiered biochemical signaling pathway[1] is highly conserved and has several characteristic properties, all of which are significantly affected by ATP concentration.



Future directions

The cellular environment is not homogeneous, even with respect to ATP distribution.



ATP has to diffuse from the mitochondria to the cell surface to participate in reactions that involve membrane-bound proteins.

ATP participates in many reactions at the cell membrane (e.g., generation of cyclic AMP (cAMP), a second messenger in cell-cell signaling).

- How does the mitochondrial geometry affect ATP spatio-temporal dynamics?
- How does the spatial distribution of ATP in the cell affect production of cAMP?
- How does cAMP compartmentalization affect the activation of transcription factors in the nucleus?

References

[1] C.Y. Huang and J.E. Ferrell. *Proc. Nat. Acad. Sci* 93 (1996), 10078–10083.
[2] U.S. Bhalla and R. Iyengar. *Science* 283:5400 (1999), 381–387.

We acknowledge funding from an NSF CiBER-IGERT Fellowship (to J.A.N.) and the University of California Chancellor's Postdoctoral Fellowship (to P.R.).