



Mathematical Modelling of the Canonical Nf-Kappab Pathway

Janina Mothes

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The regulation of the transcription factor NF-kappaB plays a central role in physiological processes by influencing cell differentiation, proliferation and survival. Experiments revealed great differences in the dynamical behaviour of NF-kappaB ranging from sustained oscillations to damped oscillations and monotone increase evolving to a stable steady state. In this work, a theoretical approach was used to determine internal sources of the observed variability in the dynamics. A core model of the canonical NF-kappaB pathway was developed to study the dynamical properties using a bifurcation analysis. The total NF-kappaB concentration as well as the transcription rate constant of the NF-kappaB inhibitor IkappaBalphawere identified as two key parameters that influence the dynamics of NF-kappaB. Further, the activation and deactivation of NF-kappaB is tightly regulated by negative feed-back loops. The transcription of the two NF-kappaB inhibitors IkappaBalphaand A20 is induced by NF-kappaB itself. In this work, a mathematical model was developed comprising both negative feedbacks to determine if post-transcriptional regulation of the two inhibitor mRNAs by the RNA-binding protein RC3H1 can impact the NF-kappaB signal transduction. Additionally, the interplay of the two feedbacks was analysed and cell type specific differences were examined. Again, the total NF-kappaB concentration was found to have a crucial impact. It determines the influence of RC3H1 on the NF-kappaB activity and the interplay of the two feedbacks.

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