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Effects of delay and noise in a negative feedback regulatory motif MATTEO PALASSINI, University of Barcelona, MARTA DIES, Laboratori de Bioquimica i Biofisica Computacional, Institut Municipal d'Investigacio Medica, Barcelona — The small copy number of the molecules involved in gene regulation can induce nontrivial stochastic phenomena such as noise-induced oscillations. An often neglected aspect of regulation dynamics are the delays involved in transcription and translation. Delays introduce analytical and computational complications because the dynamics is non-Markovian. We study the interplay of noise and delays in a negative feedback model of the p53 core regulatory network. Recent experiments have found pronounced oscillations in the concentrations of proteins p53 and Mdm2 in individual cells subjected to DNA damage. Similar oscillations occur in the Hes-1 and NK-kB systems, and in circadian rhythms. Several mechanisms have been proposed to explain this oscillatory behaviour, such as deterministic limit cycles, with and without delay, or noise-induced excursions in excitable models. We consider a generic delayed Master Equation incorporating the activation of Mdm2 by p53 and the Mdm2-promoted degradation of p53. In the deterministic limit and for large delays, the model shows a Hopf bifurcation. Via exact stochastic simulations, we find strong noise-induced oscillations well outside the limit-cycle region. We propose that this may be a generic mechanism for oscillations in gene regulatory systems.

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