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Supporting Material

Harmonic Oscillations in Homeostatic Controllers: Dynamics of the p53 Regulatory System

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- SUPPORTING MATERIAL -
Harmonic Oscillations in Homeostatic Controllers: Dynamics of the p53 Regulatory System

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Computational Methods

Rate equations were solved numerically by using the FORTRAN subroutine LSODE (Livermore Solver of Ordinary Differential Equations) (1) and MATLAB (www.mathworks.com). Molecular noise was implemented into the model by the FORTRAN subroutine RAN1 (2). To make notations simpler, concentrations are denoted by their names without square brackets.

Kinetics of scaffold-supported degradation of p53 by Mdm2

We consider four rapid equilibria between scaffold C, $p53$, and $Mdm2$ (Fig. 3b):

$$p53 + C \rightleftarrows C \cdot p53; \qquad K_A = \frac{p53\ C}{(C{\cdot}p53)} \tag{1}$$

$$Mdm2 + C \rightleftarrows Mdm2 \cdot C; \qquad K_B = \frac{Mdm2\ C}{(Mdm2{\cdot}C)} \tag{2}$$

$$Mdm2{\cdot}C + p53 \rightleftarrows Mdm2{\cdot}C{\cdot}p53; \quad K_{BA} = \frac{(Mdm2{\cdot}C)\ p53}{(Mdm2{\cdot}C{\cdot}p53)} \tag{3}$$

$$C{\cdot}p53 + Mdm2 \rightleftarrows Mdm2{\cdot}C{\cdot}p53; \quad K_{AB} = \frac{(C{\cdot}p53)\ Mdm2}{(Mdm2{\cdot}C{\cdot}p53)} \tag{4}$$

The total amount of scaffold C_0 can be written as:

$$\begin{aligned} C_0 &= C + C{\cdot}p53 + Mdm2{\cdot}C + Mdm2{\cdot}C{\cdot}p53 \\ &= Mdm2{\cdot}C{\cdot}p53 \left\{ \frac{K_A}{p53}\frac{K_{AB}}{Mdm2} + \frac{K_{AB}}{Mdm2} + \frac{K_{BA}}{p53} + 1 \right\} \end{aligned} \tag{5}$$

Assuming that C_0 is constant and that the degradation velocity v_{degr}^{p53} of $p53$ is proportional to the amount of the ternary complex, i.e., $v_{degr}^{p53} = k'{\cdot}(Mdm2{\cdot}C{\cdot}p53)$, we get:

$$v_{degr}^{p53} = \frac{k'C_0}{\frac{K_A}{p53}\frac{K_{AB}}{Mdm2} + \frac{K_{AB}}{Mdm2} + \frac{K_{BA}}{p53} + 1} \tag{6}$$

Kinetics of p53 induced Mdm2 synthesis

We consider a rapid equilibrium of p53 binding at the Mdm2 promoter region, where the corresponding dissociation constant between bound and unbound p53 is denoted by $K^{p53}_{d,mdm2prom}$. Assuming simple saturation behavior the rate of Mdm2-mRNA ($mdm2$) and the synthesis rate of the Mdm2-protein can be formulated as follows:

$$\frac{dmdm2}{dt} = \frac{k_{transcr} p53}{K^{p53}_{d,mdm2prom} + p53} - k^{mdm2}_{degr} \times mdm2 \tag{7}$$

$$(\frac{dMdm2}{dt})_{synth} = k_{transl} \times mdm2 \tag{8}$$

Assuming further that Mdm2-mRNA is in a steady state by setting Eq. 7 to zero, gives the following expression for the rate of Mdm2 synthesis:

$$(\frac{dMdm2}{dt})_{synth} = \frac{k_{transl} k_{transcr}}{k^{mdm2}_{degr}} \times \frac{p53}{K^{p53}_{d,mdm2prom} + p53} \tag{9}$$

In the case p53 binds weakly at the Mdm2 promoter, Eq. 9 becomes first-order with respect to p53 as written in Eq. 9 in the main text:

$$(\frac{dMdm2}{dt})_{synth} = \frac{k_{transl} k_{transcr}}{k^{mdm2}_{degr}} p53 = k^{Mdm2}_{s} p53 \tag{10}$$

Random variation of rate constants

Rate constants k_i were randomly varied between a minimum value $k_{i,min}$ and a maximum value $k_{i,max}$ by using the relationship

$$k_i = k_{i,min} + (k_{i,max} - k_{i,min}) \cdot r \tag{11}$$

where r is a random number between zero and one generated by the Fortran subroutine RAN1 (2). Table 1 in the main text provides an overview of the regions in which the individual rate constants were varied. Because during integration of the rate equations separate calls for r are made for each rate constant at every time step, rate constants have different random variation profiles (see Fig. 1 below).

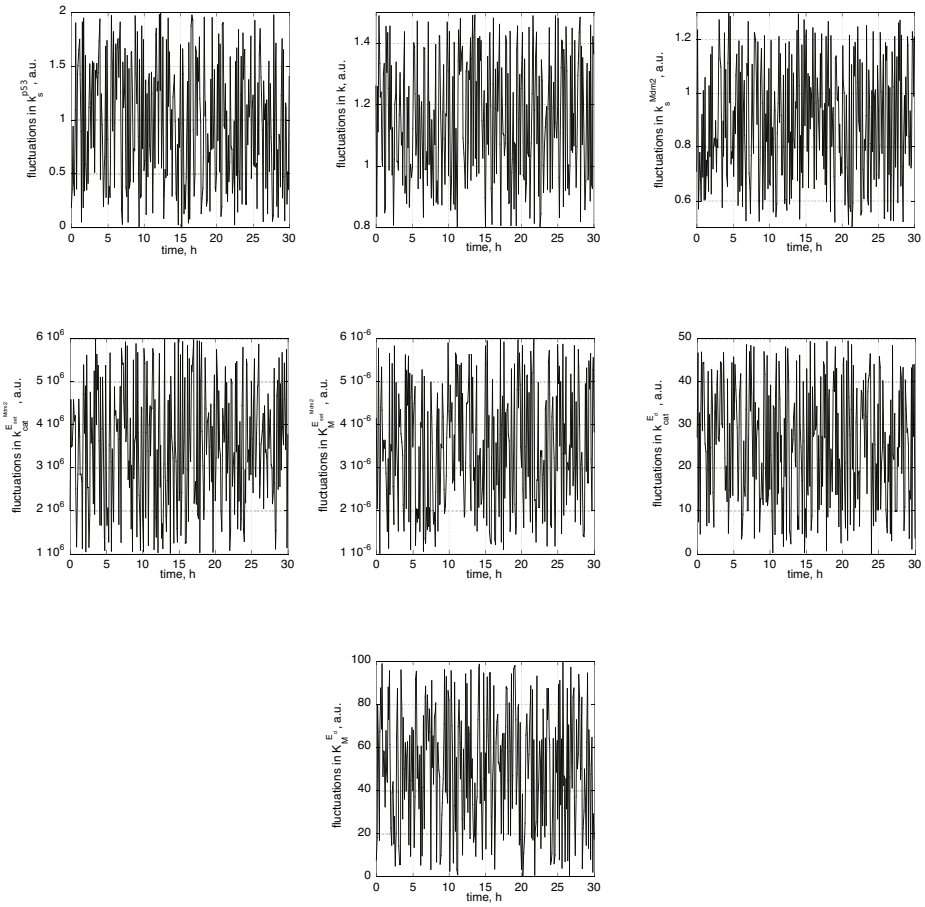

Figure 1: Random variation of rate constants

k_i	$k_{i,min}$	$k_{i,max}$
k_s^{p53}	0.0	2.0
k	0.8	1.5
k_s^{Mdm2}	0.5	1.3
$k_{cat}^{E_{set}^{Mdm2}}$	1×10^6	6×10^6
$K_M^{E_{set}^{Mdm2}}$	1×10^{-6}	6×10^{-6}
$k_{cat}^{E_d}$	0.0	50.0
$K_M^{E_d}$	0.0	100.0

Table 1: Random variation of rate constants

References

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