

Supporting Material, File S3 Text

Frequency switching between oscillatory  
homeostats and the regulation of p53

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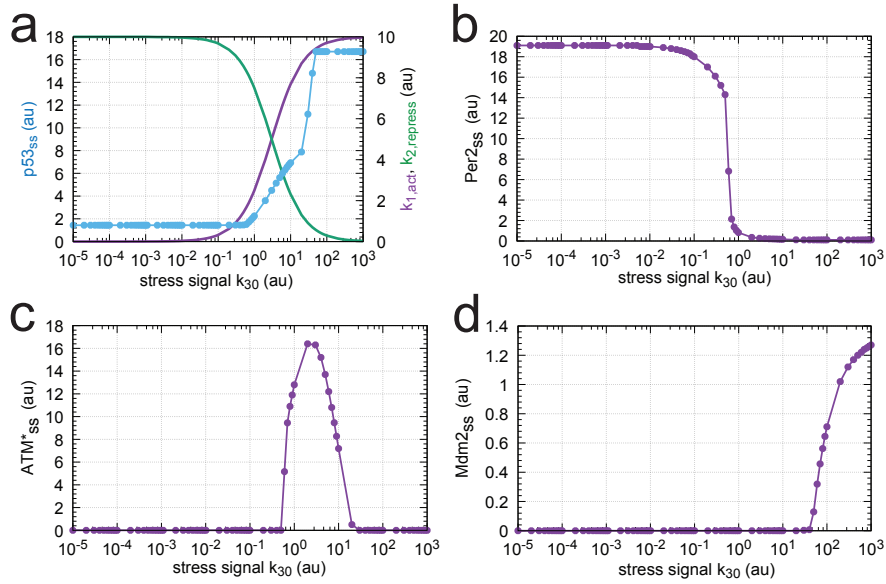
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### Steady state levels of model (Fig 7) as a function of stress parameter $k_{30}$ when feedback loops are non-oscillatory

When the degradation reactions of the controlled variable p53 become first-order with respect to p53, Eq 11 changes to

$$\begin{aligned} \dot{p53} = & k_{31} + \frac{k_1 k_{30}}{K_{as} + k_{30}} - \left( \frac{K_{Is}}{K_{Is} + k_{30}} \right) + k_{29} \cdot ATM^* + k_6 \cdot Per2 \\ & - \left( \frac{K_{I2}}{K_{I2} + Per2} \right) \cdot Mdm2 \end{aligned} \quad (S1)$$

and the integral p53-controllers Per2, ATM\*, and Mdm2 lose their oscillatory behaviors.



**Figure S1.** Change of steady state levels of model (Fig 7) as a function of stress parameter  $k_{30}$  when degradation of p53 is first-order with respect to p53 (Eq S1). Shown levels are (a) p53,  $k_{1,act}$ ,  $k_{2,inh}$ ; (b) Per2; (c) ATM\*; (d) Mdm2. Rate constants as in Fig 8. Initial concentrations:  $p53_0=1.44$ ,  $Mdm2_0=9.44 \times 10^{-8}$ ,  $Per2_0=19.1$ ,  $Bmal/Clk_0=0.7$ ,  $Per1_0=16.27 \times 10^{-2}$ ,  $Per1 \cdots Per2_0=1.20$ ,  $(Per1_2)_0=7.87 \times 10^{-2}$ ,  $(Per2_2)_0=3.65 \times 10^{-6}$ ,  $ATM_0^*=2.09 \times 10^{-10}$ . Step-length (LSODE)= $1 \times 10^{-2}$ , simulation time 3000 time units (h).

Fig S1 shows the steady state levels of p53, Per2, ATM\*, and Mdm2 for different stress levels  $k_{30}$  when using Eq S1 for p53. All other rate equations remain unchanged. While p53 set-points do not change, controller levels and the rheostatic p53 levels with respect to the control by ATM\* are slightly altered in comparison with Fig 8 when controllers are in oscillatory mode. Note that higher stress levels are needed for Mdm2 to take control over p53. Fig S2 shows the steady state levels of p53 and the Per2 as a function of time and the stress level  $k_{30}$ . Note that Per2 concentrations are non-oscillatory when Per2 takes part in the control of p53. However, when the other feedback loops control p53 Per2 levels are low and become entrained by the circadian Bmal/Clk oscillator.

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**Figure S2.** (*following page*) Non-oscillatory steady state levels of p53 and Per2 at different stress levels  $k_{30}$ . Parameter values are the same as in Fig S1. (a)  $k_{30}=1\times 10^{-4}$ . Per2 determines the concentration of p53. Initial concentrations:  $p53_0=1.44$ ,  $Mdm2_0=9.44\times 10^{-8}$ ,  $Per2_0=1.91\times 10^1$ ,  $Bmal/Clk_0=0.7$ ,  $Per1_0=6.27\times 10^{-2}$ ,  $(Per1\cdots Per2)_0=1.20$ ,  $(Per1_2)_0=7.87\times 10^{-2}$ ,  $(Per2_2)_0=3.65\times 10^{-1}$ ,  $ATM_0^*=2.09\times 10^{-10}$ . (b)  $k_{30}=1\times 10^{-1}$ . Initial concentrations:  $p53_0=1.44$ ,  $Mdm2_0=9.44\times 10^{-8}$ ,  $Per2_0=1.80\times 10^1$ ,  $Bmal/Clk_0=0.7$ ,  $Per1_0=6.83\times 10^{-2}$ ,  $(Per1\cdots Per2)_0=1.23$ ,  $(Per1_2)_0=9.33\times 10^{-2}$ ,  $(Per2_2)_0=3.24\times 10^{-1}$ ,  $ATM_0^*=2.53\times 10^{-7}$ . (c)  $k_{30}=1.0$ . The ATM\* controller has taken over and controls p53 levels. Initial concentrations:  $p53_0=2.25$ ,  $Mdm2_0=1.56\times 10^{-7}$ ,  $Per2_0=1.29\times 10^{-5}$ ,  $Bmal/Clk_0=1.34$ ,  $Per1_0=3.98\times 10^{-1}$ ,  $(Per1\cdots Per2)_0=5.14\times 10^{-6}$ ,  $(Per1_2)_0=2.54$ ,  $(Per2_2)_0=1.67\times 10^{-13}$ ,  $ATM_0^*=13.37$ . (d)  $k_{30}=10.0$ . ATM\* still controls p53 levels. Initial concentrations:  $p53_0=6.92$ ,  $Mdm2_0=7.11\times 10^{-7}$ ,  $Per2_0=1.76\times 10^{-6}$ ,  $Bmal/Clk_0=1.32$ ,  $Per1_0=2.71\times 10^{-1}$ ,  $(Per1\cdots Per2)_0=4.76\times 10^{-7}$ ,  $(Per1_2)_0=0.875$ ,  $(Per2_2)_0=3.09\times 10^{-15}$ ,  $ATM_0^*=7.284$ . (e)  $k_{30}=100.0$ . Mdm2 controls the level of p53. Initial concentrations:  $p53_0=16.67$ ,  $Mdm2_0=7.03\times 10^{-1}$ ,  $Per2_0=6.26\times 10^{-7}$ ,  $Bmal/Clk_0=1.09$ ,  $Per1_0=1.78\times 10^{-1}$ ,  $(Per1\cdots Per2)_0=1.11\times 10^{-7}$ ,  $(Per1_2)_0=0.286$ ,  $(Per2_2)_0=3.92\times 10^{-16}$ ,  $ATM_0^*=1.10\times 10^{-6}$ .

