Stochastic model of p53 regulation

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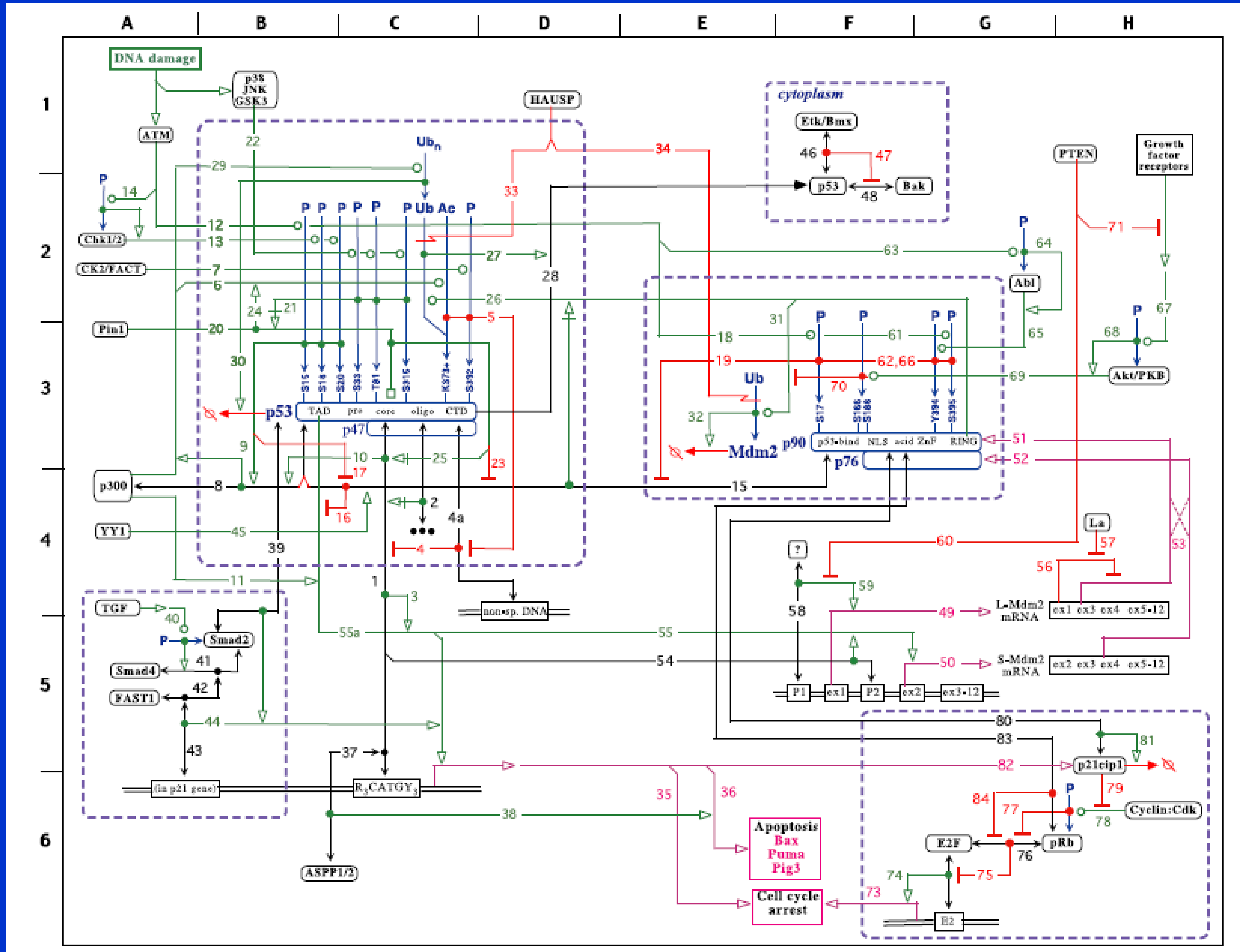
Why p53?

- p53 is a transcription factor that regulates hundreds of resposible for
  - DNA repair,
  - cell cycle arrest
  - apoptosis (programmed cell death)

- p53 is mutated (or absent) in 50% of solid tumors,
  in other 50% gene controlling p53 are mutated.

- 50 000 experimental citations, less than 100 theoretical papers

It is difficult !



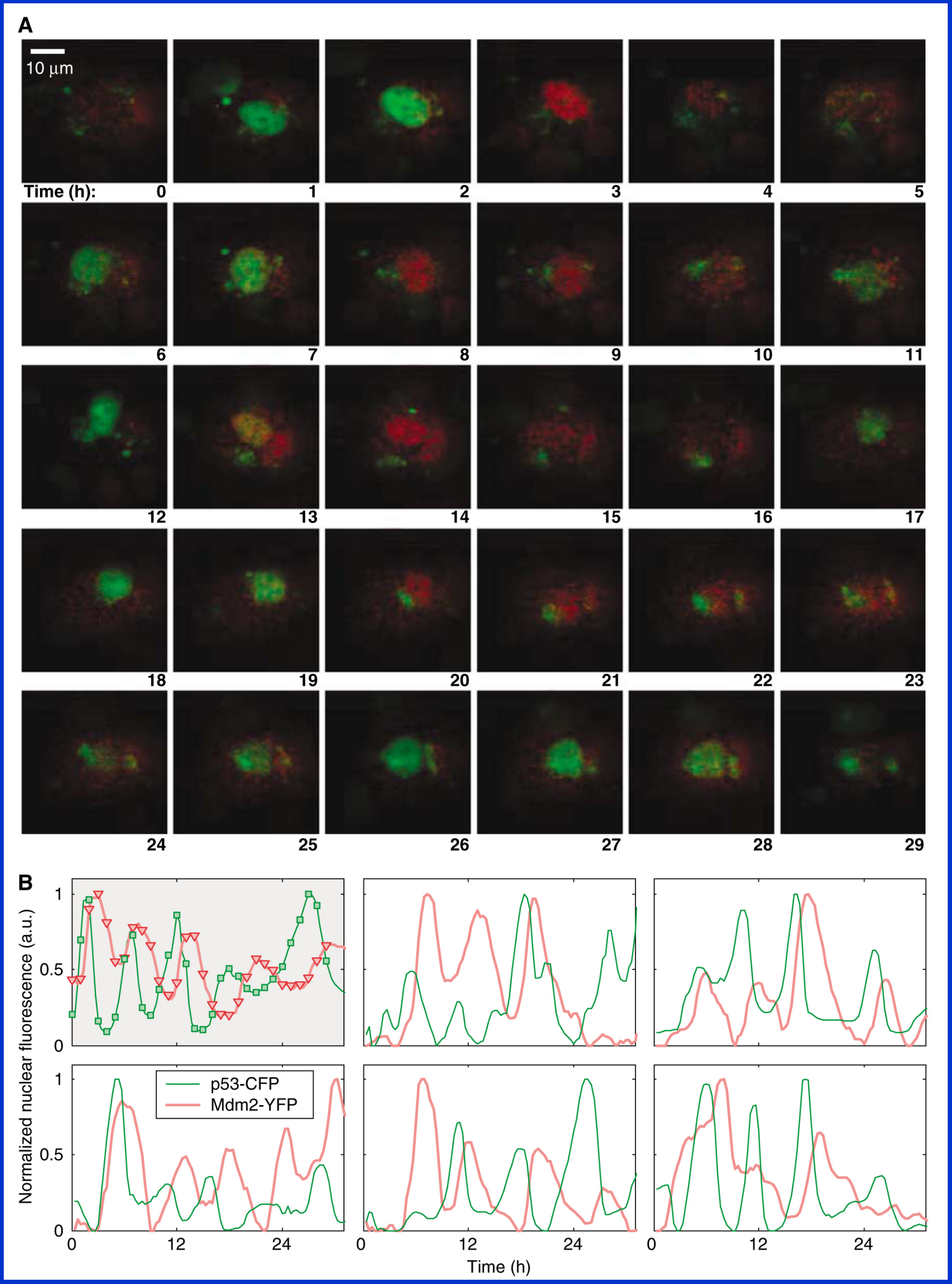
10 or more feedbacks,
100 or more components,
Stochastic noise

Kohn and Pommier 2005

Experiments

- proteins and mRNA levels, kinase activity
- System perturbations
  - gene, mRNA, protein knockouts
  - protein (gene) modifications
- Various stimulation protocols

Single cell experiment
(Geva-Zatorski et al. 2006)

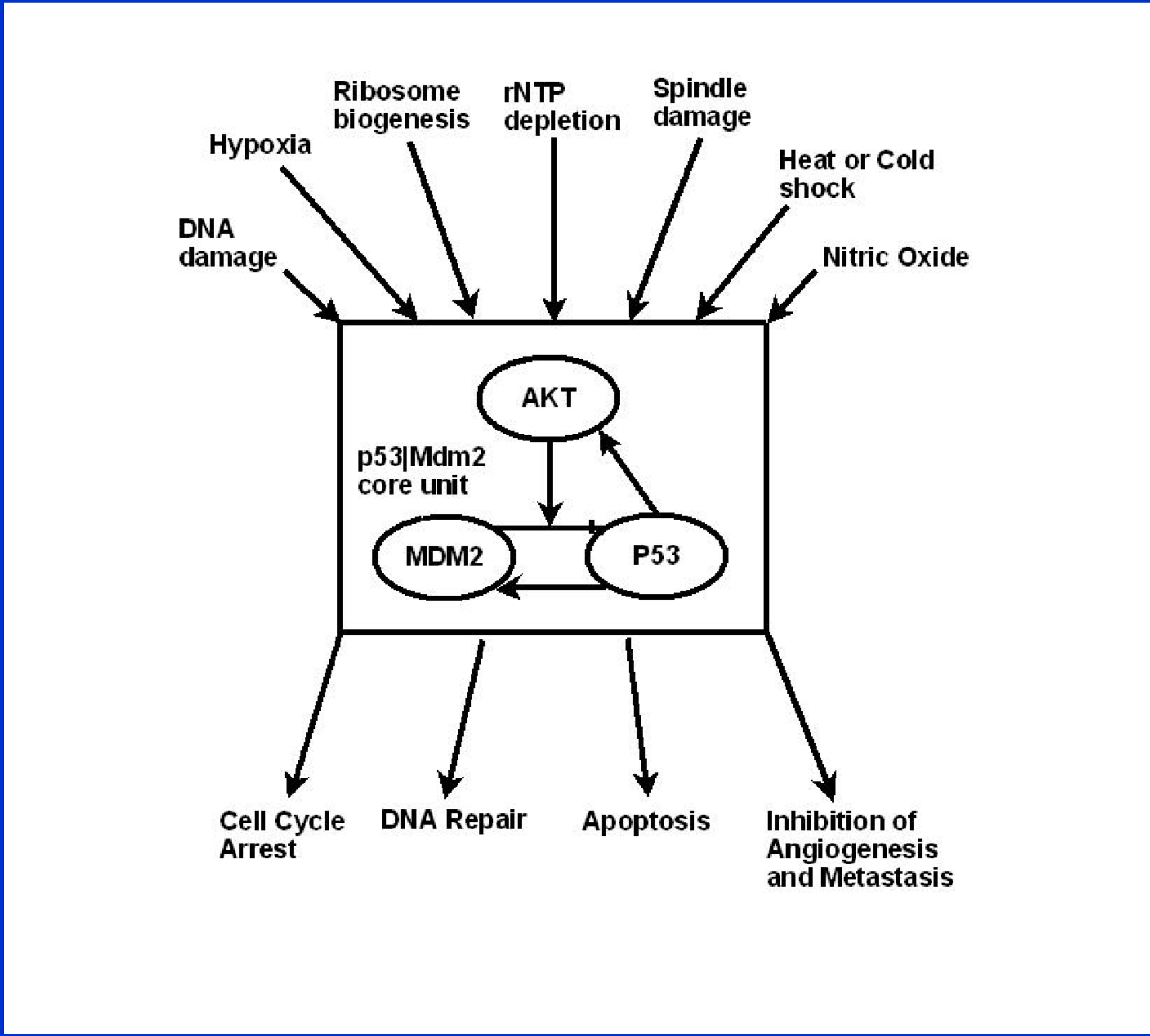


- continuous oscillations for 72 hour after gamma irradiation

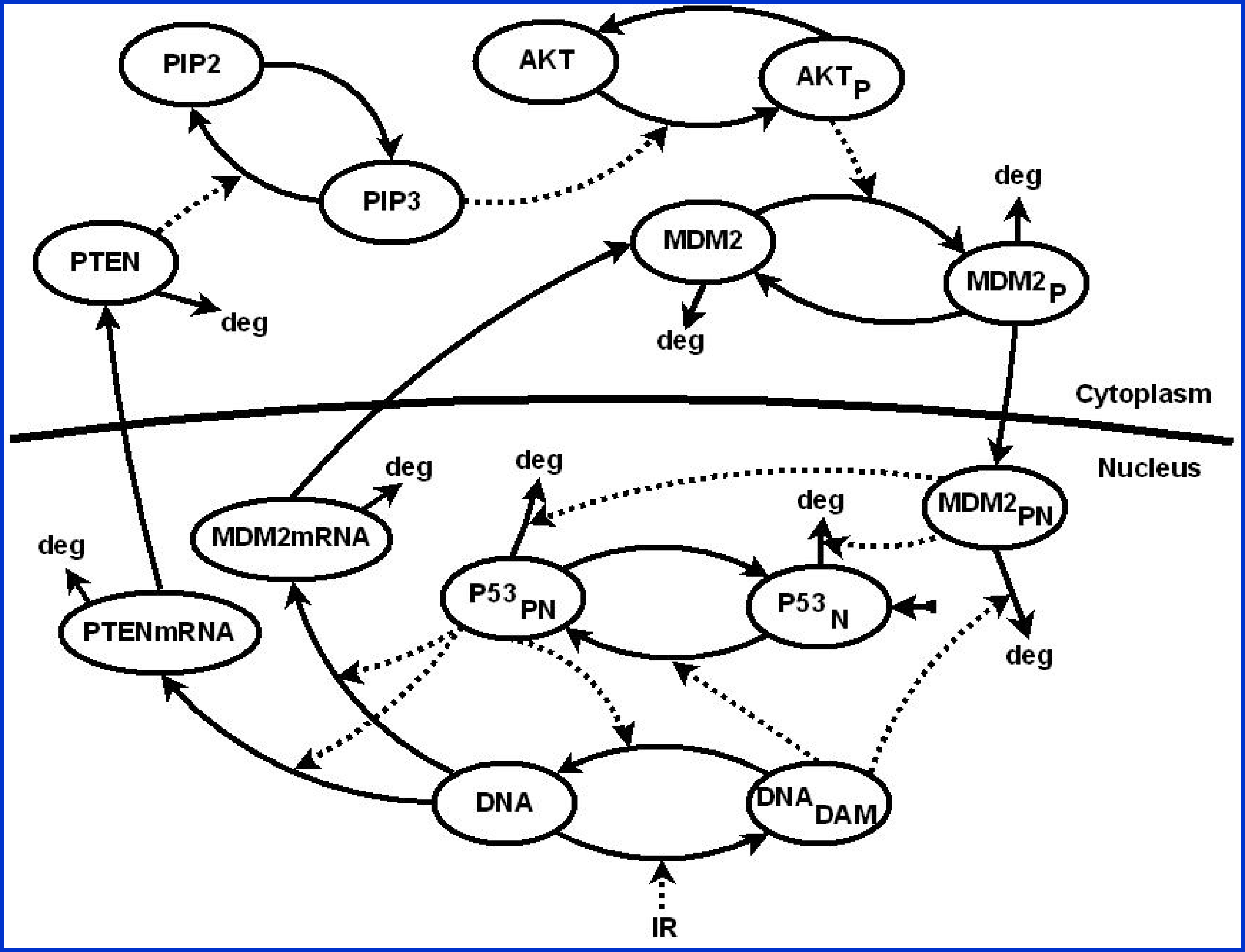
- fraction of oscillating cells increases with gamma dose reaching about 60% for 10 Gy.

- even after 10 Gy dose, analyzed cells proliferated

Inputs and outputs

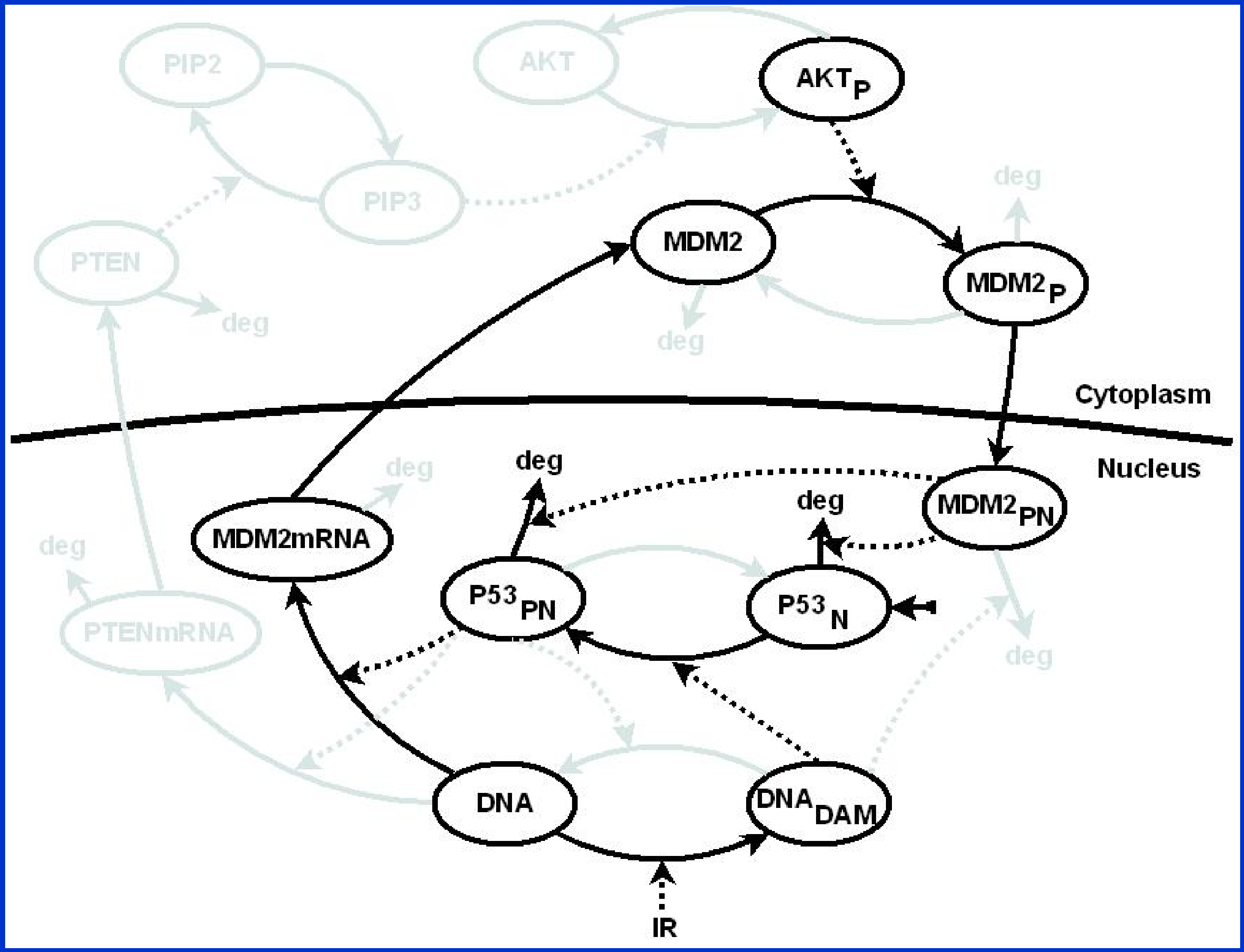


"Our pathway"

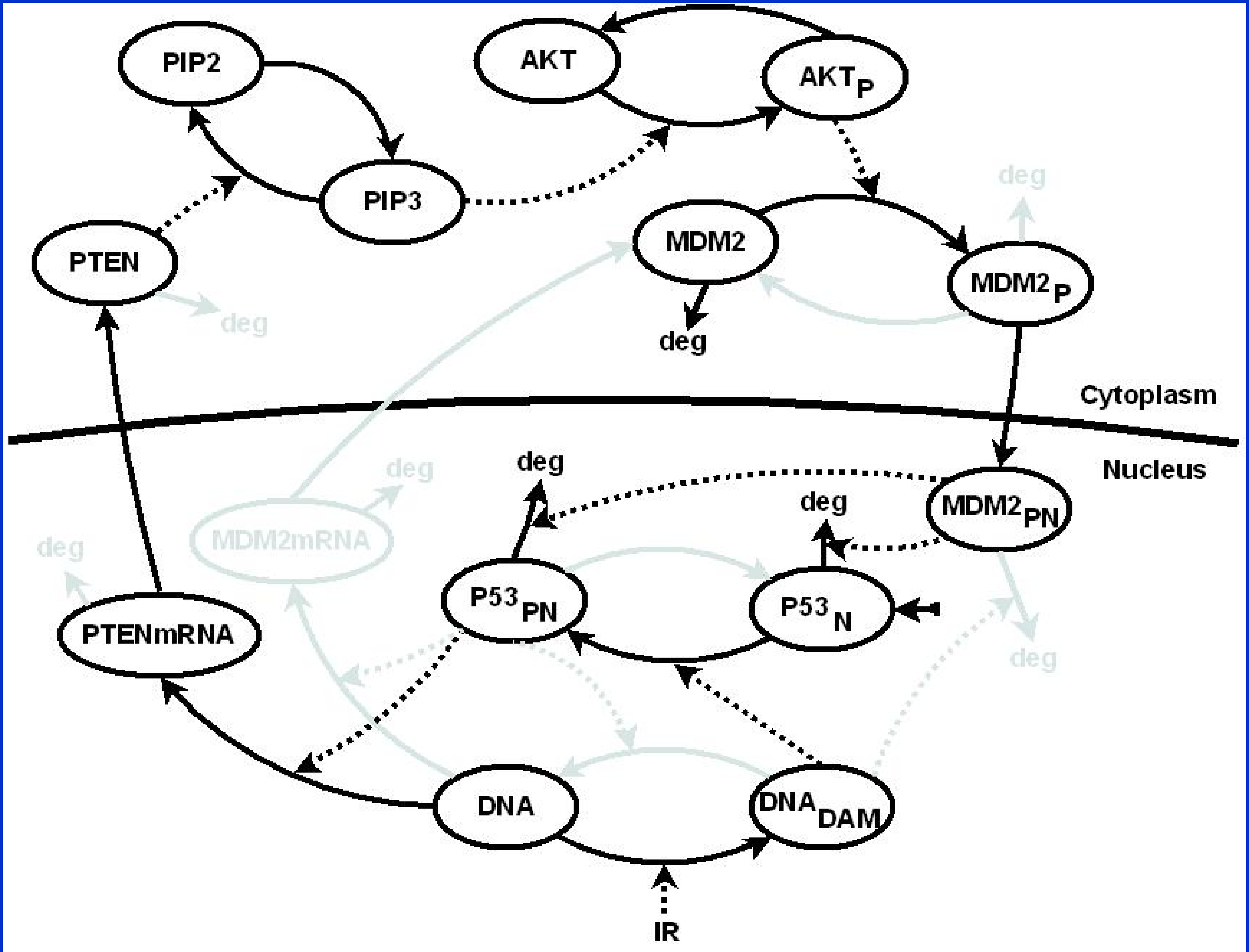


PIP2
AKT
AKTP
PIP3
deg
MDM2
PTEN
MDM2P
deg
deg
Cytoplasm
Nucleus
deg
deg
MDM2PN
deg
MDM2mRNA
deg
P53PN
P53N
PTENmRNA
deg
DNA
DNADAM
IR

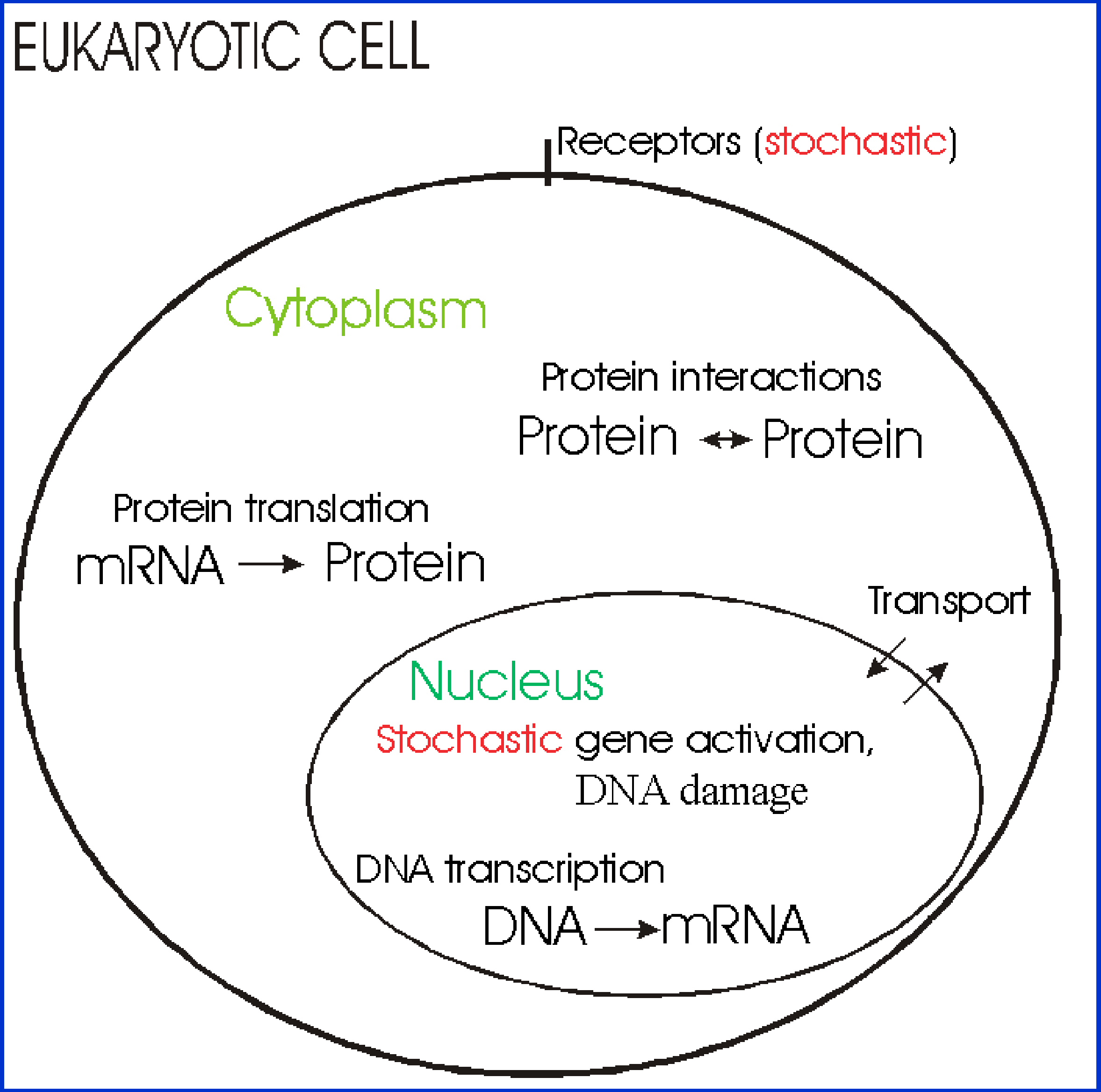
Negative feedback loop



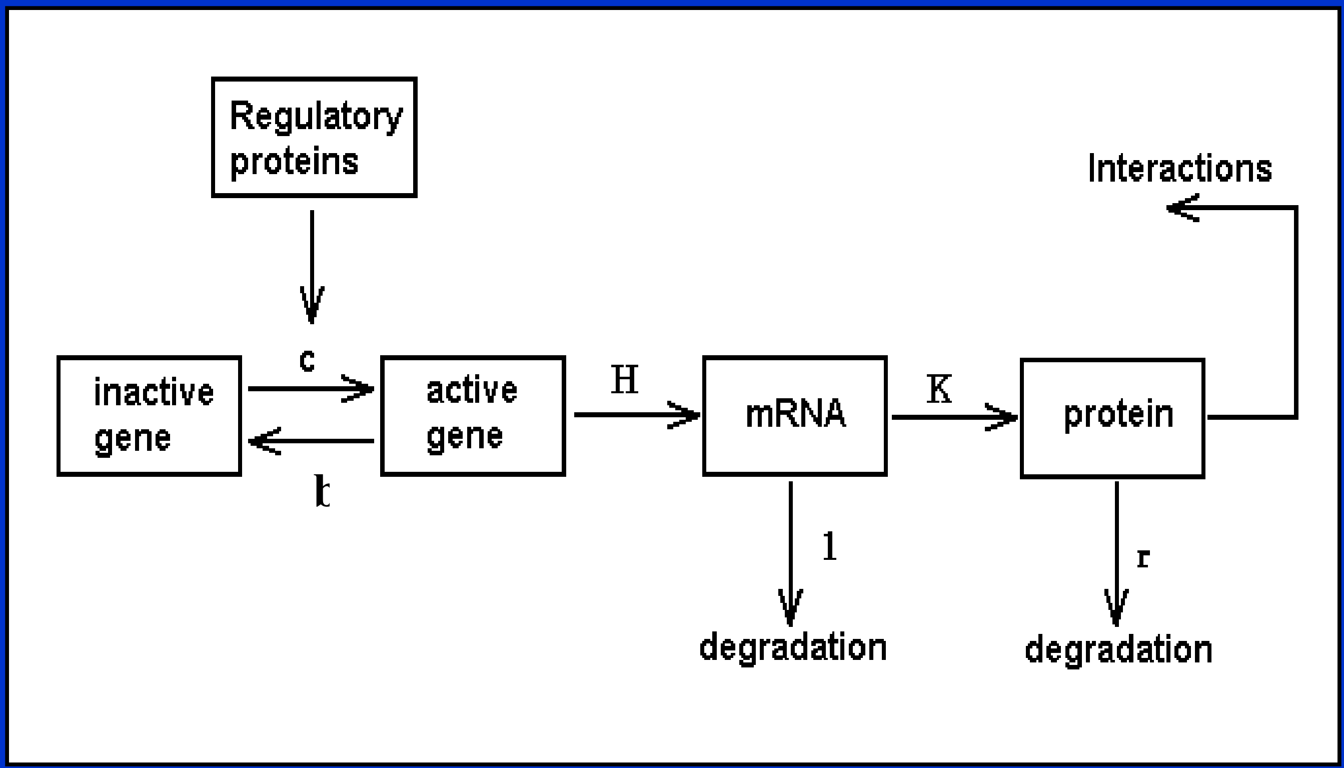
Positive feedback loop



Stochasticity in eukaryotic cell regulation

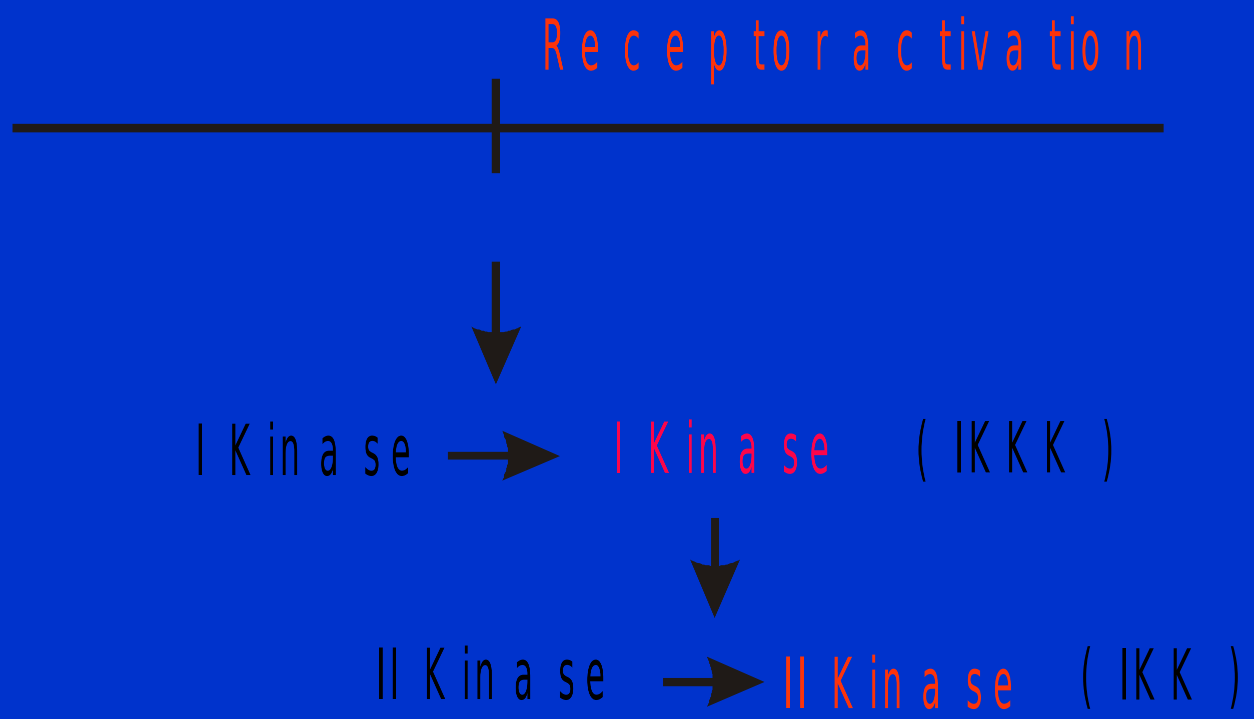


Stochastic gene expression



The main steps in gene expression

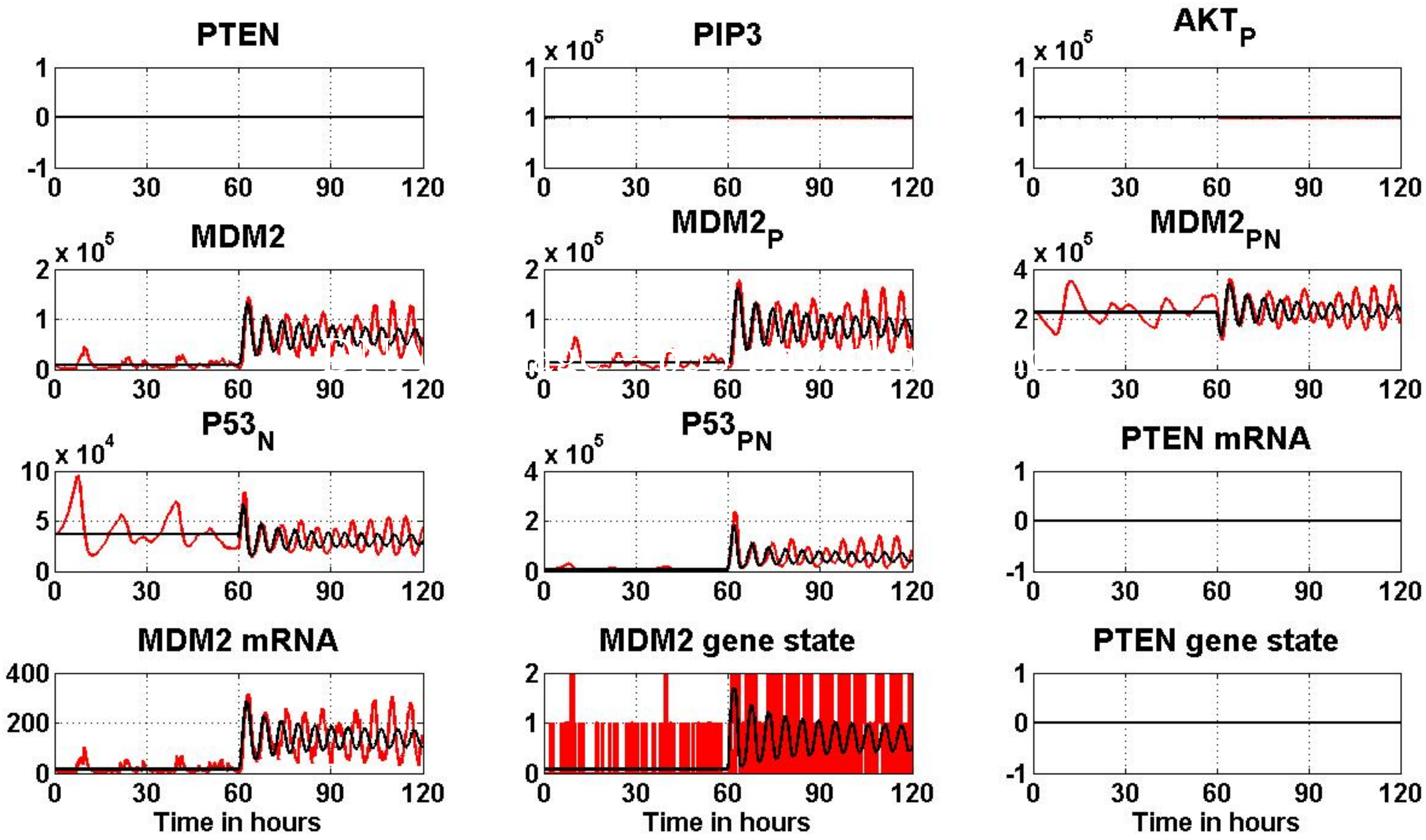
Transduction amplification pathway



Stochastic receptor activation may result in a large number of II kinase molecules.

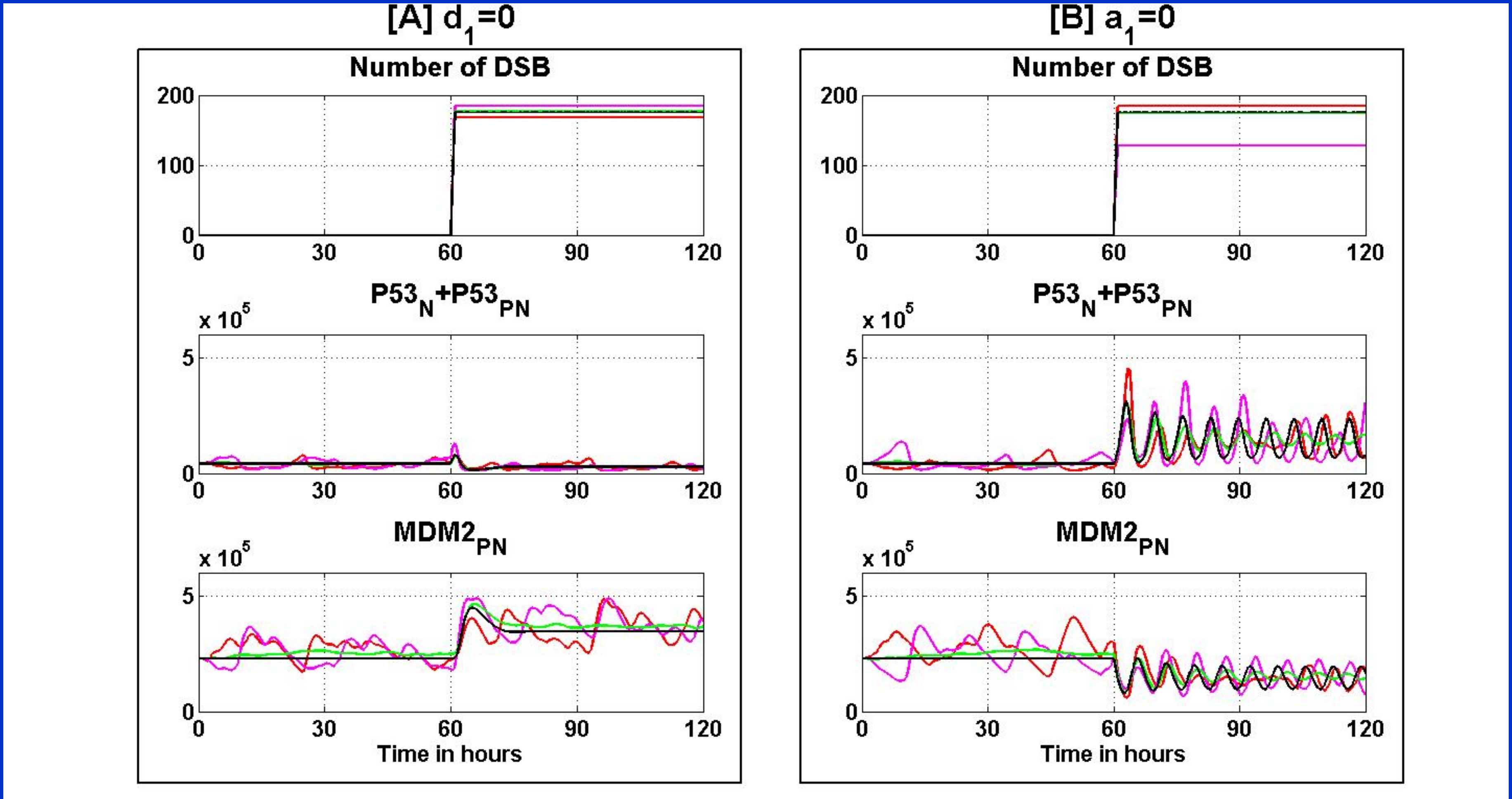
No PTEN (positive feedback blocked); No DNA repair

Oscillations



DNA damage = p53 phosphorylation + MDM2 degradation

No PTEN (positive feedback blocked); No DNA repair



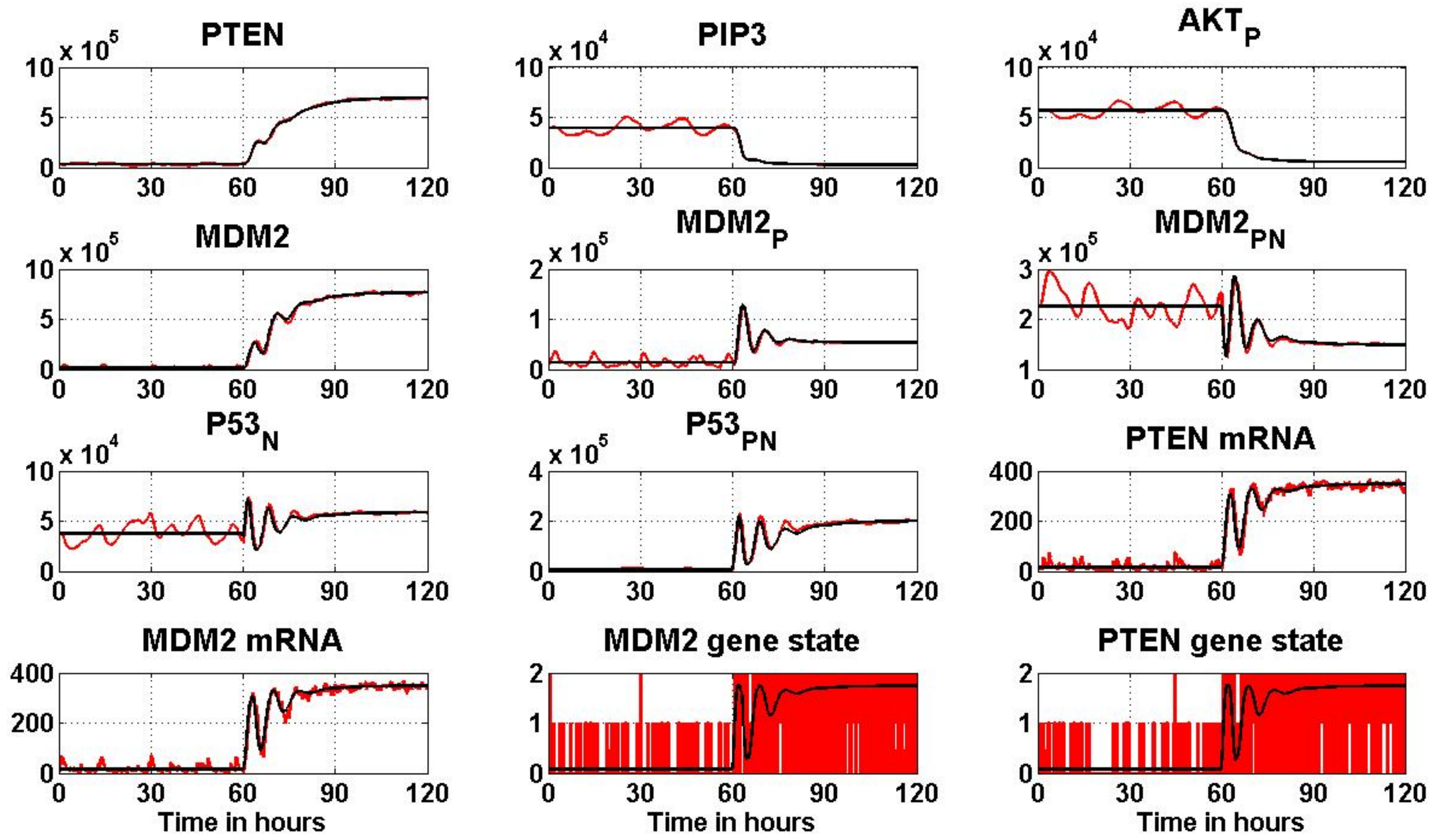
DNA damage = p53 phosphorylation

DNA damage = MDM2 degradation

oscillations

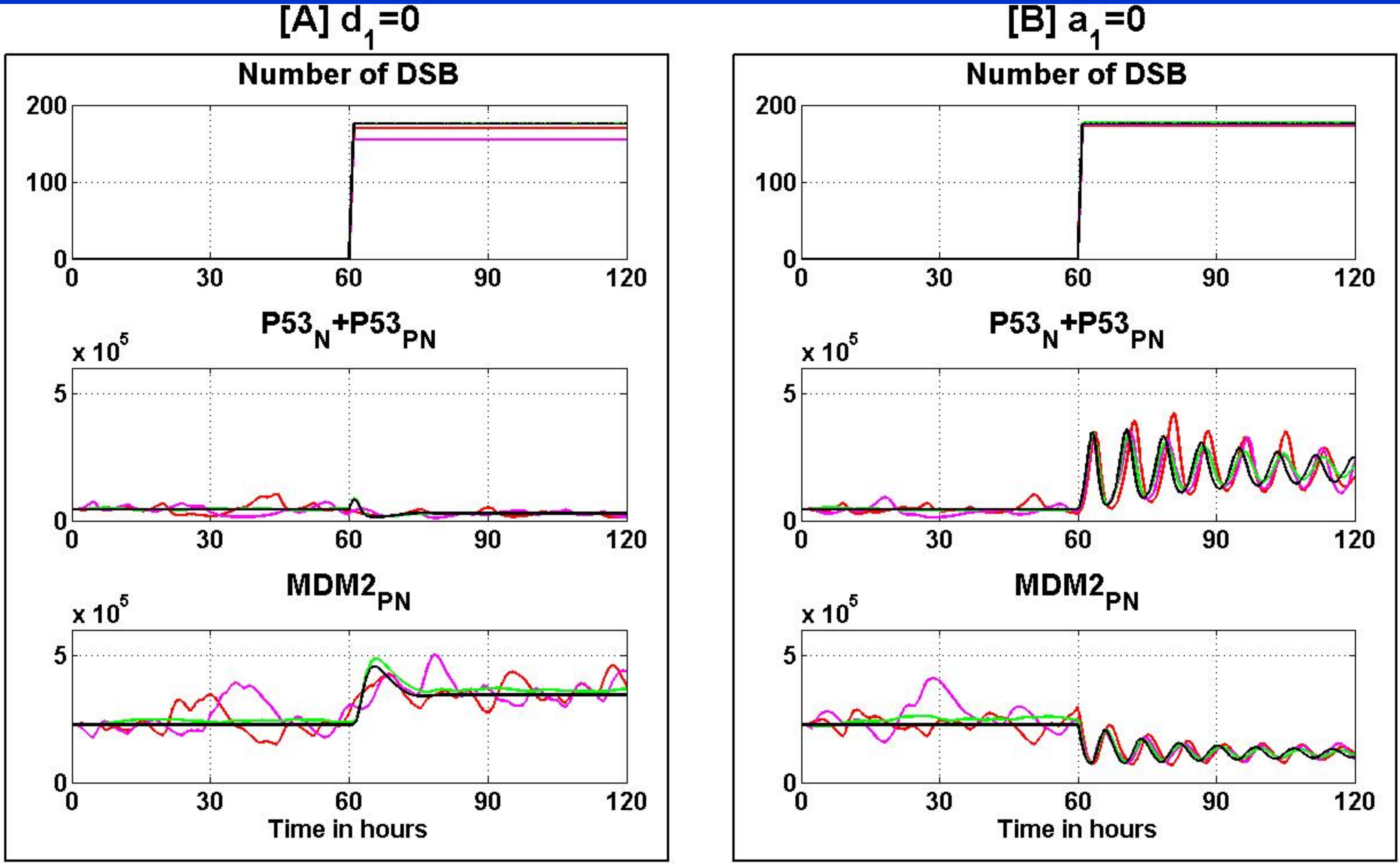
PTEN *ON* (positive feedback active); No DNA repair

Apoptosis



DNA damage = p53 phosphorylation + MDM2 degradation

PTEN *ON* (positive feedback active); No DNA repair



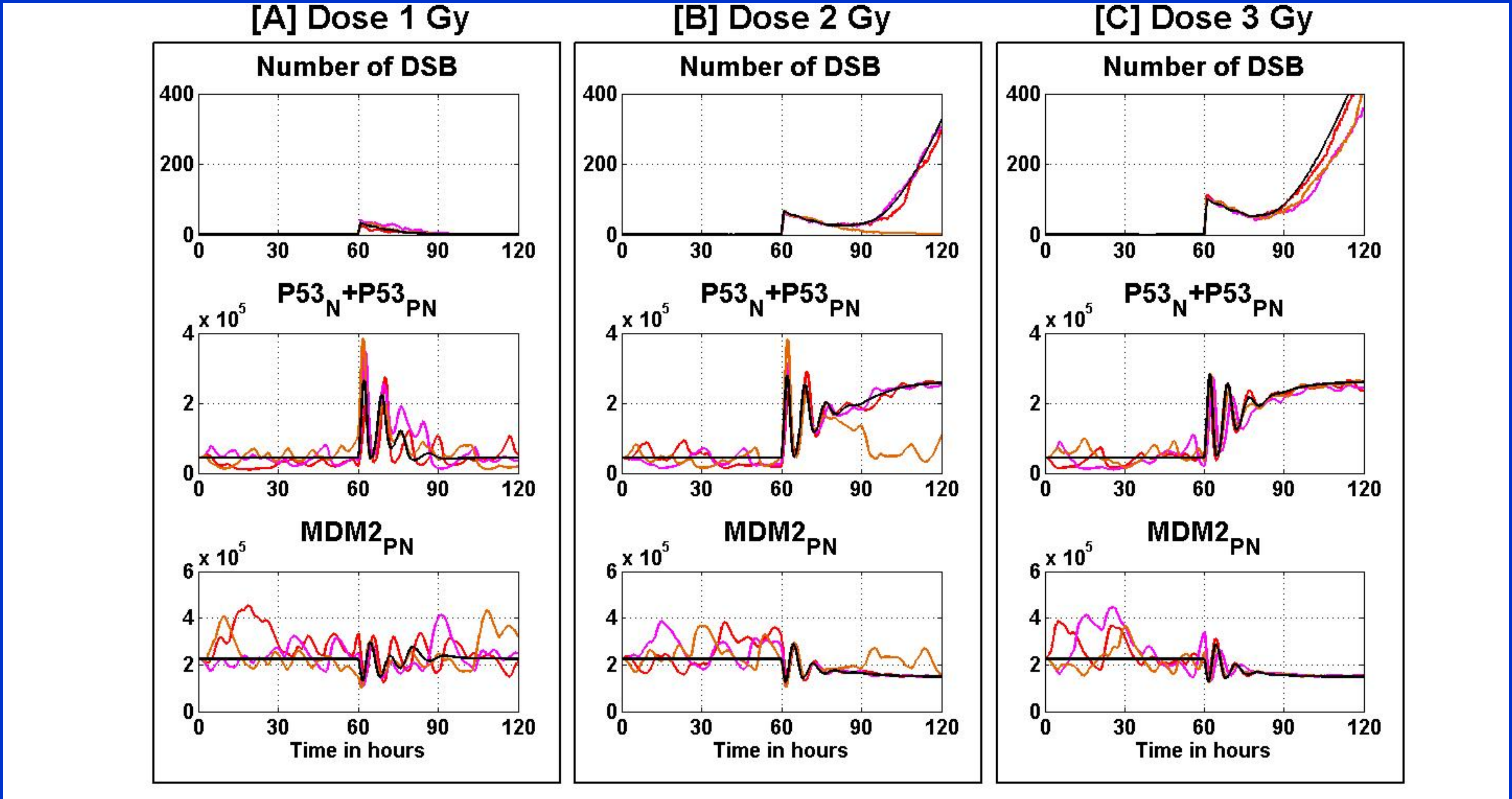
DNA damage = p53 phosphorylation

DNA damage = MDM2 degradation

oscillations

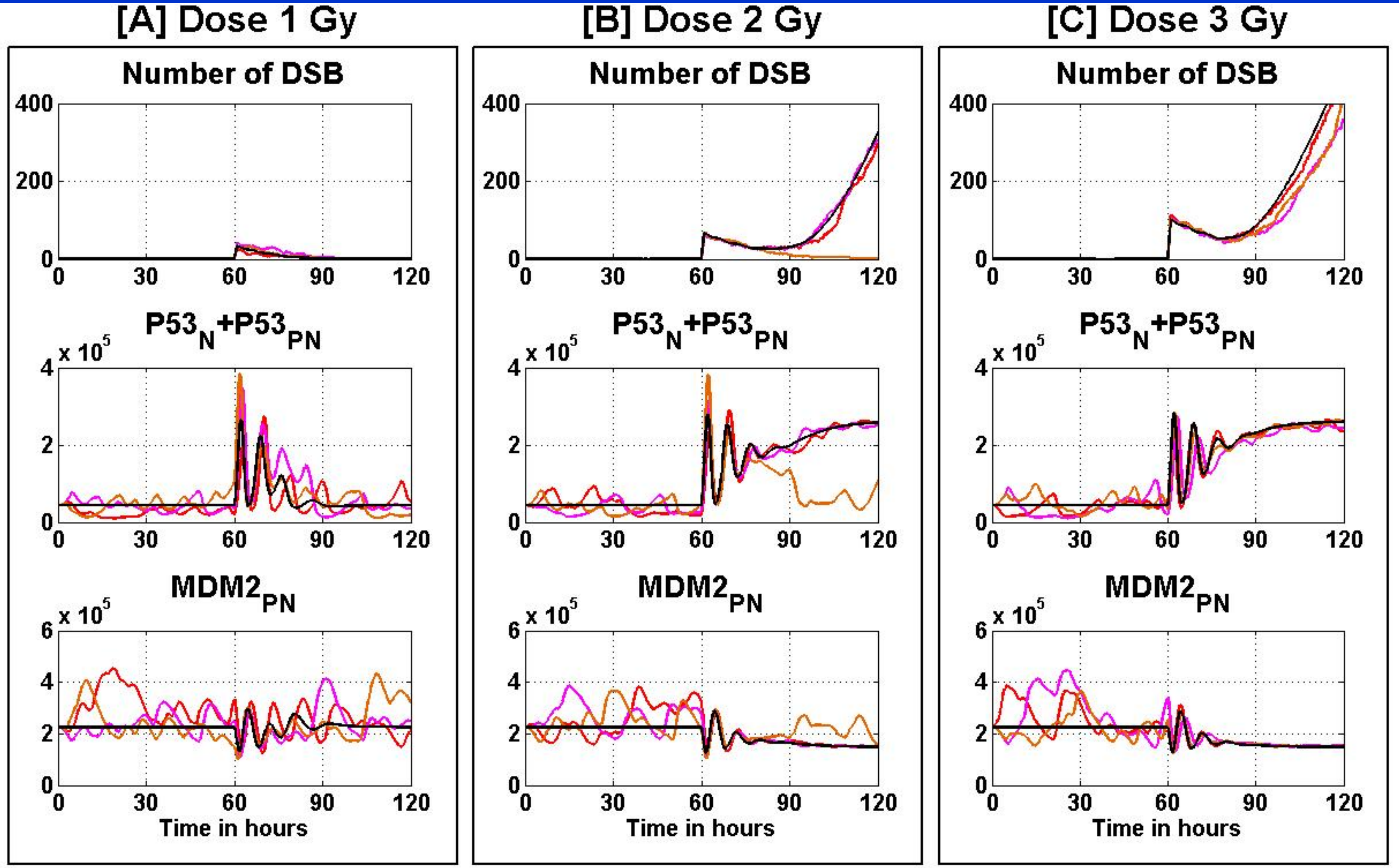
PTEN *ON* (positive feedback active); DNA repair *ON*

cell fate decision

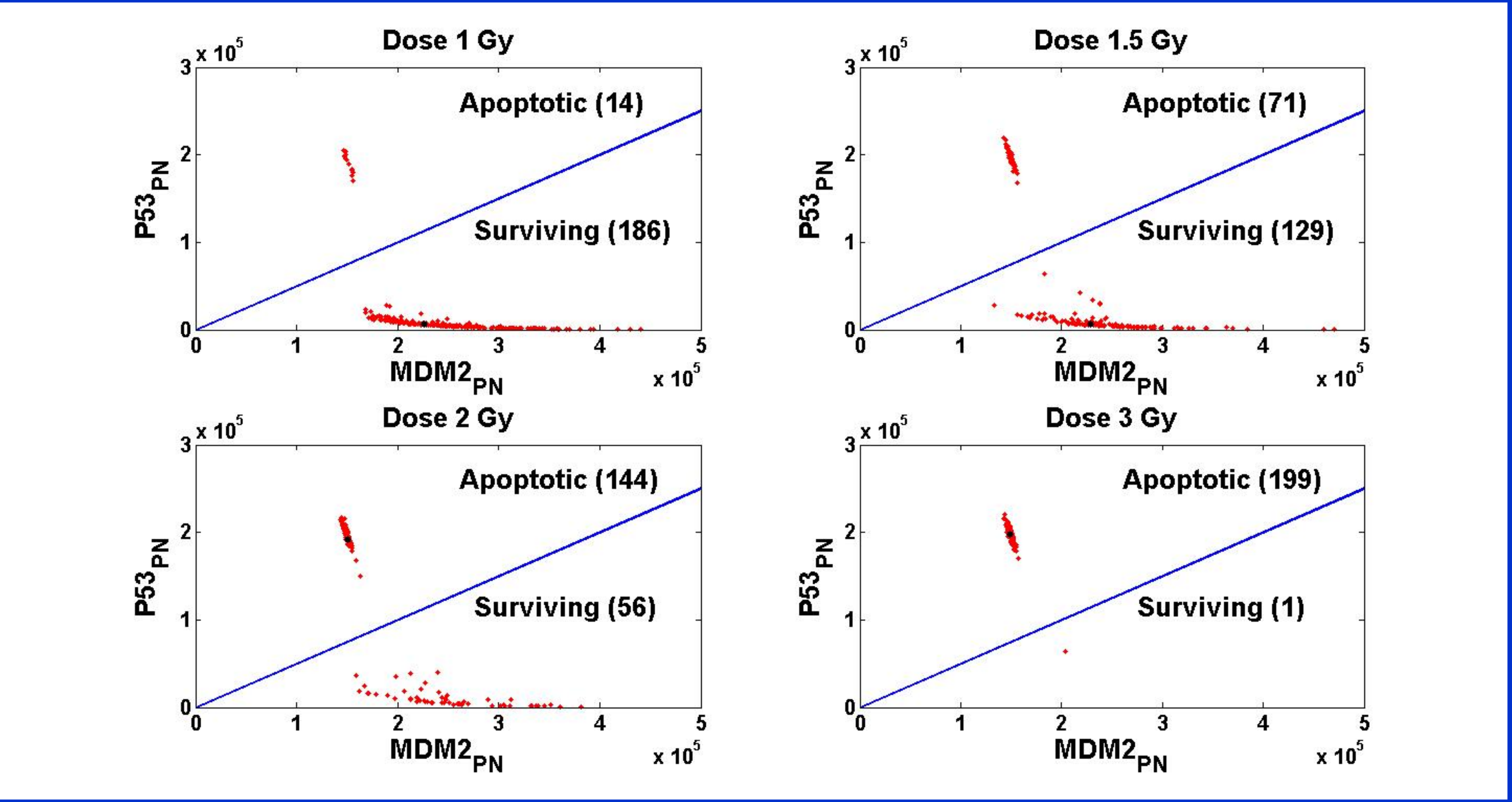


p53 produces proapoptotic factor, which cut DNA

Cell fate decision



Cell population separates into surviving and apoptotic cells 48 hours after gamma radiation.



ODEs

$$\frac{d}{dt} PTEN(t) = t_1\, PTEN_t(t) - d_2\, PTEN(t).$$

$$\frac{d}{dt} PIP_p(t) = a_2\, \left(PIP_{tot} - PIP_p(t)\right)\, - c_0\, PTEN(t)\, PIP_p(t).$$

$$\frac{d}{dt} AKT_p(t) = a_3\, \left(AKT_{tot} - AKT_p(t)\right)\, PIP_p(t) - c_1\, AKT_p(t).$$

$$\begin{aligned}\frac{d}{dt} MDM(t) \quad &= \quad t_0\, MDM_t(t) + c_2\, MDM_p(t) \\ &\quad -a_4\, MDM(t)\, AKT_p(t) - \left(d_0 + d_1\, \frac{N^2(t)}{h_0^2 + N^2(t)}\right)\, MDM(t).\end{aligned}$$

$$
\begin{aligned}
\frac{d}{dt}MDM_p(t) \quad &= \quad a_4\, MDM(t)\, AKT_p(t) - c_2\, MDM_p(t) - i_0\, MDM_p(t) \\
&\quad + e_0\, MDM_{pn}(t) - \left(d_0 + d_1\, \frac{N^2(t)}{h_0^2 + N^2(t)}\right)\, MDM_p(t).
\end{aligned}
$$

$$
\frac{d}{dt}MDM_{pn}(t) = i_0\, MDM_p(t) - e_0\, MDM_{pn}(t) - \left(d_0 + d_1\, \frac{N^2(t)}{h_0^2 + N^2(t)}\right)\, MDM_{pn}(t).
$$

$$
\begin{aligned}
\frac{d}{dt}P53_n(t) \quad &= \quad p_0 - \left(a_0 + a_1\, \frac{N^2(t)}{h_0^2 + N^2(t)}\right)\, P53_n(t) + c_3\, P53_{pn}(t) \\
&\quad - \left(d_3 + d_4\, MDM_{pn}^2(t)\right)\, P53_n(t).
\end{aligned}
$$

$$
\begin{aligned}
\frac{d}{dt}P53_{pn}(t) \quad &= \quad \left(a_0 + a_1\, \frac{N^2(t)}{h_0^2 + N^2(t)}\right)\, P53_n(t) - c_3\, P53_{pn}(t) \\
&\quad - \left(d_5 + d_6\, MDM_{pn}^2(t)\right)\, P53_{pn}(t).
\end{aligned}
$$

$$\frac{d}{dt}MDM_t(t) = s_0\,(G_{M1} + G_{M2}) - d_7\,MDM_t(t).$$

$$\frac{d}{dt}PTEN_t(t) = s_1\,(G_{P1} + G_{P2}) - d_8\,PTEN_t(t).$$

proapoptotic factor

$$\frac{d}{dt}A(t) = p_1\frac{q_3\,P53_{np}^2(t)}{q_4 + q_3\,P53_{np}^2(t)} - d_9A(t)$$

Transition probabilities governing dynamics of discrete variables; G_M, G_P, N

Gene activation: $$P^b(t,\Delta t) = \Delta t \times (q_0 + q_1 \times P53^2_{np}(t)).$$

Gene inactivation: $$P^d(t,\Delta t) = \Delta t \times q_2.$$

DNA damage: $$P^{DAM}(t,\Delta t) = \Delta t \times d_{DAM} \times R + \Delta t \times a_6 \left(\frac{A(t)}{A_{\max}}\right)^4$$

DNA repair: $$P^{REP}(t,\Delta t) = N(t)\frac{\Delta t \times d_{REP} \times P_A(t)}{N(t) + N_{SAT} \times P_A(t)}$$

Piece-wise deterministic, time continuous Markov process

Numerical implementation

- At the simulation time t for given A_{Mdm2}, A_{PTEN} and NB calculate total propensity function of occurence of any of the reaction

$$r(t) = r^a_{DNA} + r^d_{DNA} + r^a_{Mdm2} + r^d_{Mdm2} + r^a_{PTEN} + r^d_{PTEN}$$

- Select two random numbers p_1 and p_2 from the uniform distribution on (0,1)
- Evaluate the ODE system until time t+τ such that:

$$\log(p_1) + \int_t^{t+\tau} r(s)ds = 0$$

9. Determine which reaction occurs in time t+ τ using the inequality:

$$\sum_{i=1}^{k-1} r_i(t+\tau) < p_2 * r(t+\tau) \le \sum_{i=1}^{k} r_i(t+\tau)$$

where k is the index of the reaction to occur and $r_i(t+\tau)$ individual reaction propensities

5. Replace time t+τ by t and go back to item 1