



IBM Research

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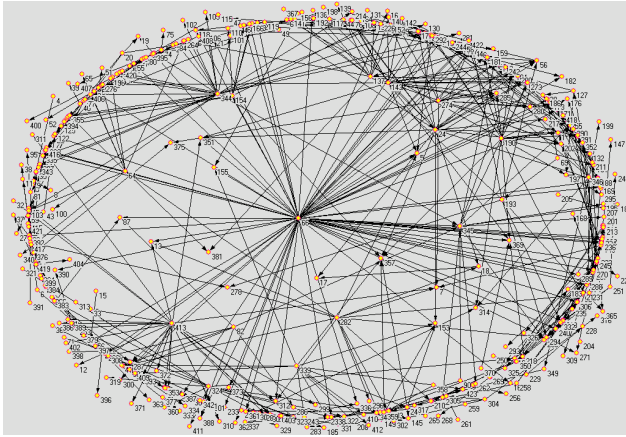
Computational Biology Center

Thomas J. Watson Research Center

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Start from a known Network Topology

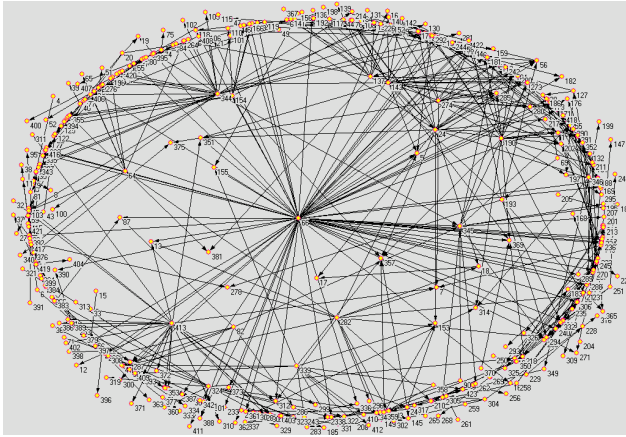
Original *E-coli* Network



518 actual connections - 423 nodes

Simulate a dynamic behavior

Original *E-coli* Network



518 actual connections - 423 nodes



simulated dynamics using
known topology

$$\frac{d}{dt} u_i = -\lambda_i u_i + \frac{\alpha_i + \sum_{j \in \mathcal{A}_i} u_j^{\gamma_{ij}}}{1 + \sum_{j \in \mathcal{A}_i} u_j^{\gamma_{ij}} + \sum_{k \in \mathcal{R}_i} u_k^{\beta_{ik}}}$$

for $i = 1, 2, \dots, N$,

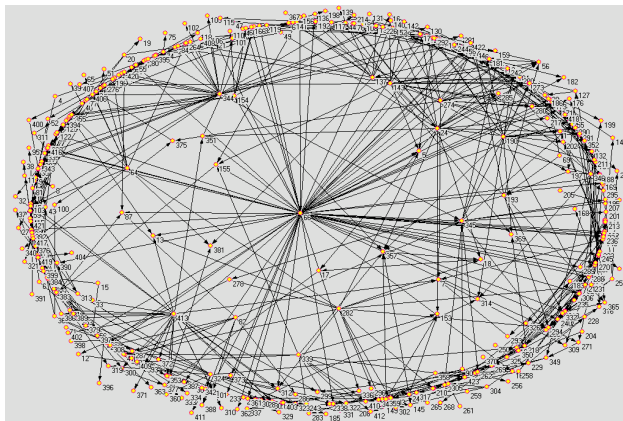
Produce a simulated gene expression
Dataset:

	Exp 1	Exp 2	Exp N
Gene 1	u_{11}	u_{12}		u_{1N}
Gene 2	u_{21}	u_{22}		u_{2N}
....				
Gene 423				

Reverse Engineer this

	Exp 1	Exp 2	Exp N
Gene 1	u_{11}	u_{12}		u_{1N}
Gene 2	u_{21}	u_{22}		u_{2N}
....				
Gene 423				

Reconstructed Network

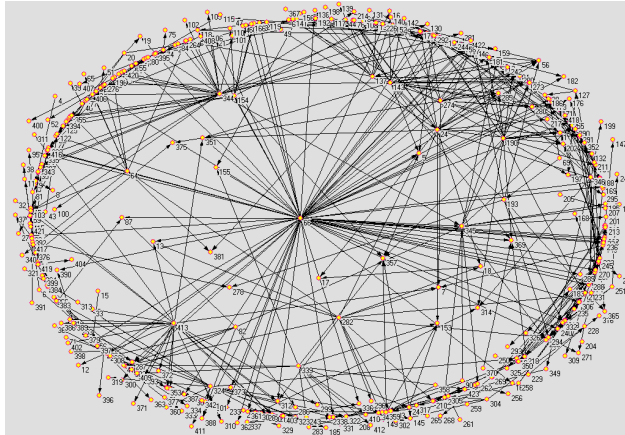


Using your favorite algorithm,
reconstructed original network
from gene expression data



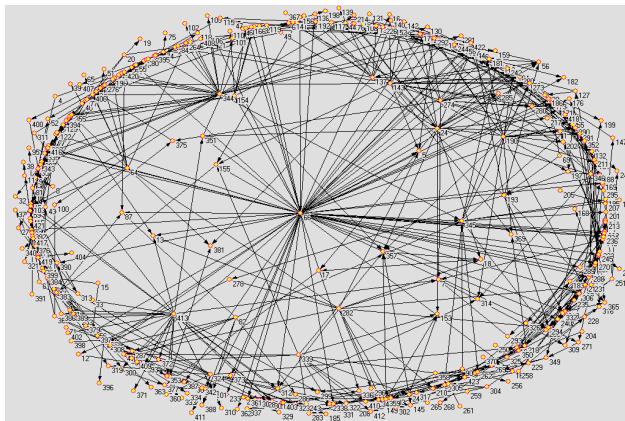
Use some metrics to compare inferred to original

Original *E-coli* Network



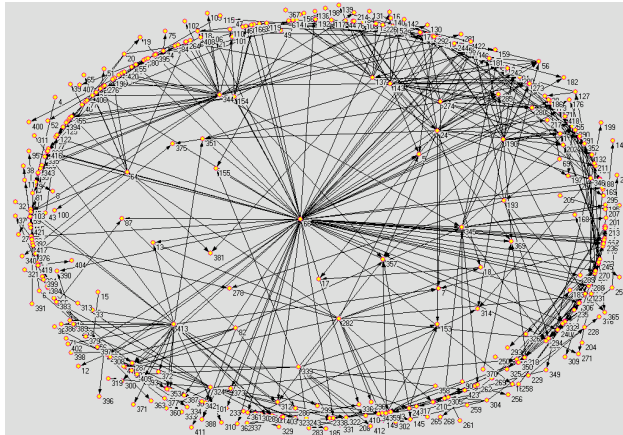
- ✍ 518 actual connections - 423 nodes
- ✍ 495 connections correctly predicted
- ✍ 85 connections wrongly predicted

Reconstructed Network



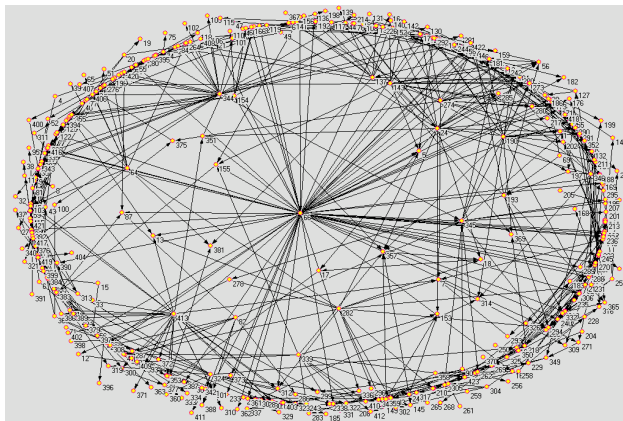
Inference of Biological Networks

Original *E-coli* Network



- ⌘ 518 actual connections - 423 nodes
- ⌘ 495 connections correctly predicted
- ⌘ 85 connections wrongly predicted

Reconstructed Network



Network topology

+ synthetic dynamics

$$\frac{d}{dt} u_i = -\lambda_i u_i + \frac{\alpha_i + \sum_{j \in \mathcal{A}_i} u_j^{\gamma_{ij}}}{1 + \sum_{j \in \mathcal{A}_i} u_j^{\gamma_{ij}} + \sum_{k \in \mathcal{R}_i} u_k^{\beta_{ik}}}$$

for $i = 1, 2, \dots, N$,

+ protocols representing actual experimental assays

+ conditional correlation algorithms (blind to original network)

= Reconstructed network

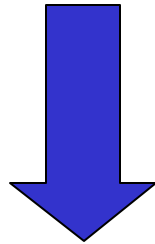


- Rice, Tu and Stolovitzky**, “Reconstructing synthetic biological network”, *Bioinformatics*, 21(6):765-73 (2005)
- Rice and Stolovitzky**, Making the most of it: Pathway reconstruction and integrative simulation using the data at hand, *Biosilico* 2(2):70-7 (2004).
- Basso, Margolin, Nemenman, Klein, Wiggins, Stolovitzky, Dalla Favera, and Califano**, Reverse engineering of regulatory networks in human B cells, 37(4):382-90 (2005).

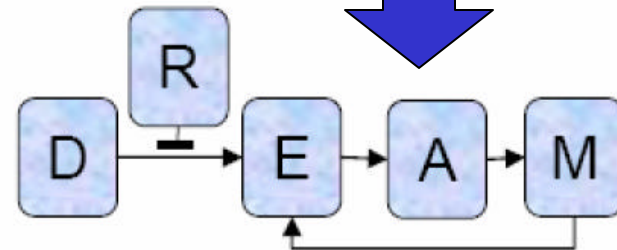
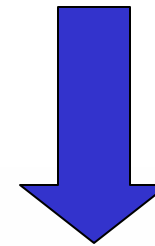
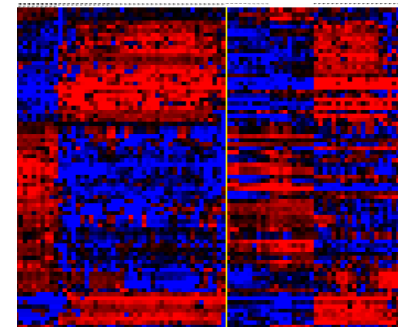
Standardized Datasets for Tool Development

Critical Assessment of Techniques for Protein Structure Prediction (CASP)

GSMLISHSDMNQQLKSAGIGFNATELHGFLSGLLCGGLKDQSWLPLLYQFSNDNHA
YPTGLVQPVTLEYEQISQTLSDVEGFTFELGLTEDENVFTQADSLSDWANQFLGIG
LAQPELAKEKGEIGEAVDDLQDICQLGYDEDDNEEELAEALEEIEYVRTIAMLFYS
HFNEGEIESKPVLH



DREAM: A Dialogue on Reverse Engineering Assessment and Methods

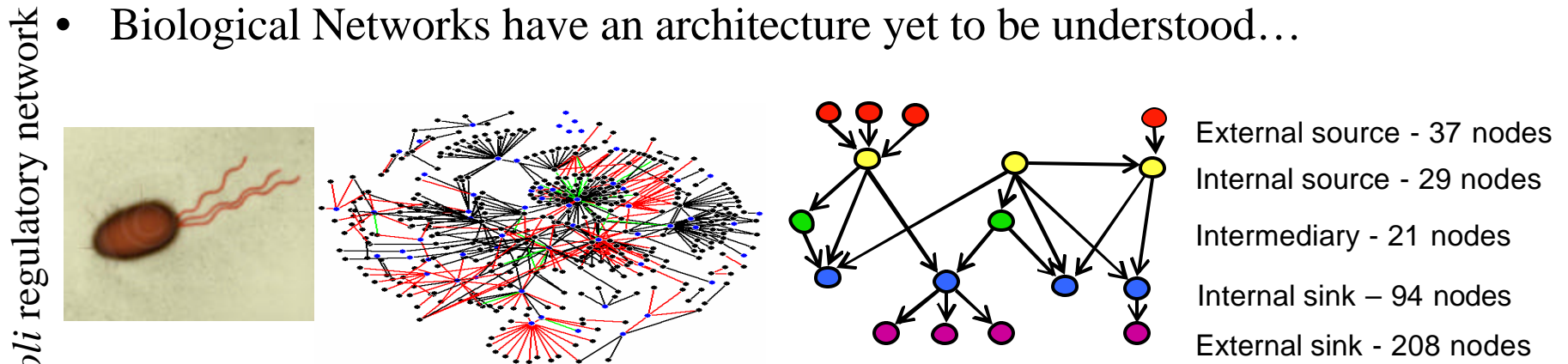


Columbia University (Andrea Califano) &
IBM Computational Biology Center (G. Stolovitzky)

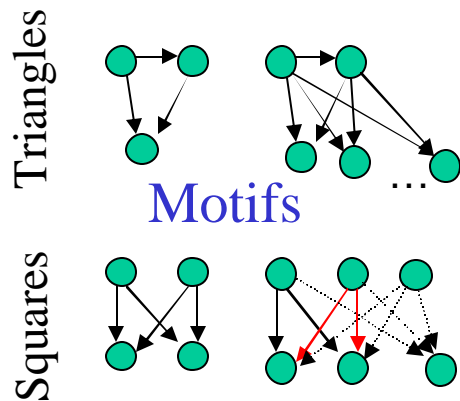
<http://www.nyas.org/dream2>

Motif Discovery in Biological Networks

- Biological Networks have an architecture yet to be understood...

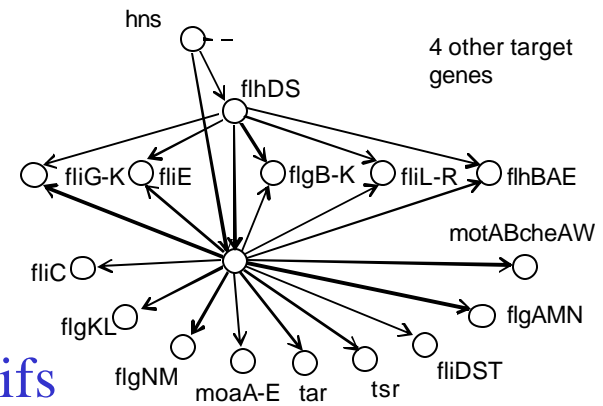


- ...and functional modules. We designed algorithms for discovery of network motifs using sub-graph isomorphism algorithms.



In *E. coli*, some functional modules are composed out of smaller motifs, such as in the flagella formation pathway.

Combination of Motifs



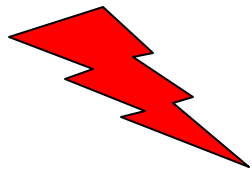
Rice, Kershenbaum and Stolovitzky. Analyzing and reconstructing gene regulatory networks. “Specialist review”, The Encyclopedia of Genetics, Genomics, Proteomics and Bioinformatics, John Wiley & Sons, Ltd:Chichester (2005).

Rice, Kershenbaum and Stolovitzky, Lasting impressions: Motifs in protein-protein maps may provide footprints of evolutionary events. Proc Natl Acad Sci USA 102: 2172-4 (2005)

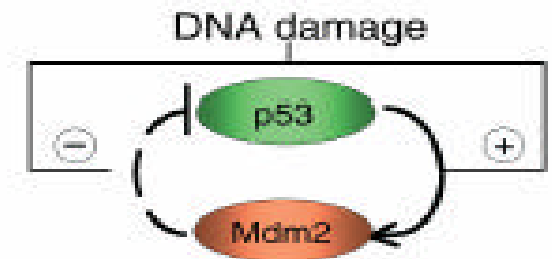
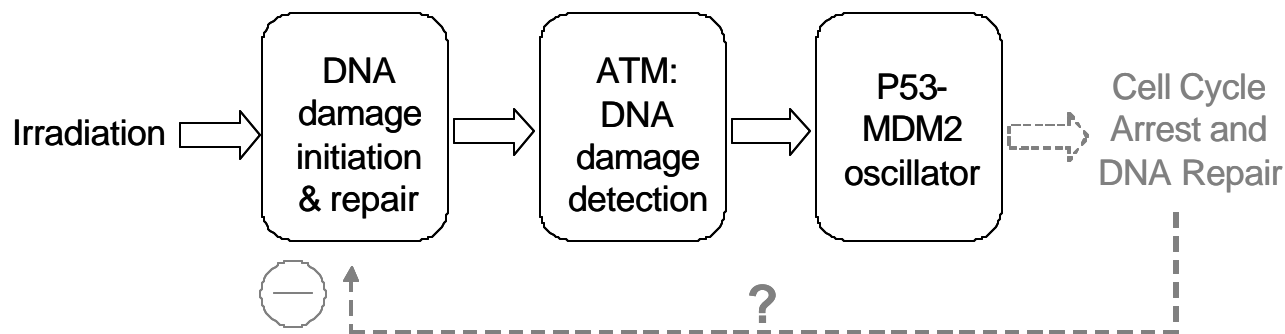
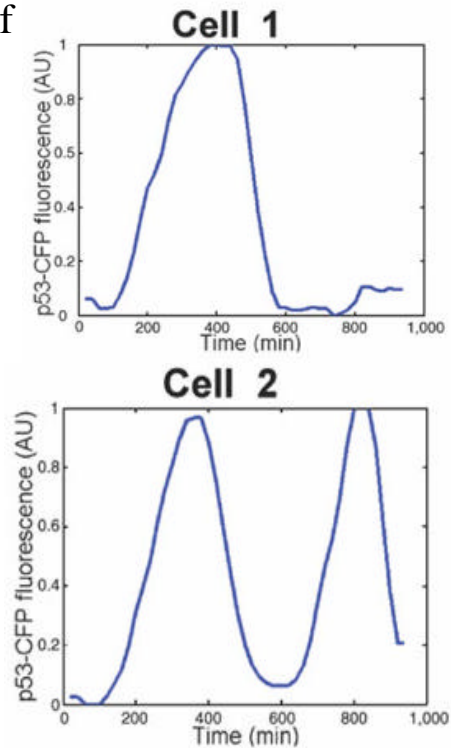
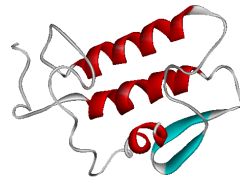
Digital response of tumor suppressor p53 to IR

Lahav, Rosenfeld, Sigal, Geva-Zatorsky, Levine, Elowitz, & Alon: Dynamics of the p53-Mdm2 feedback loop in individual cells. Nat Genet. 36: 147-50 (2004)

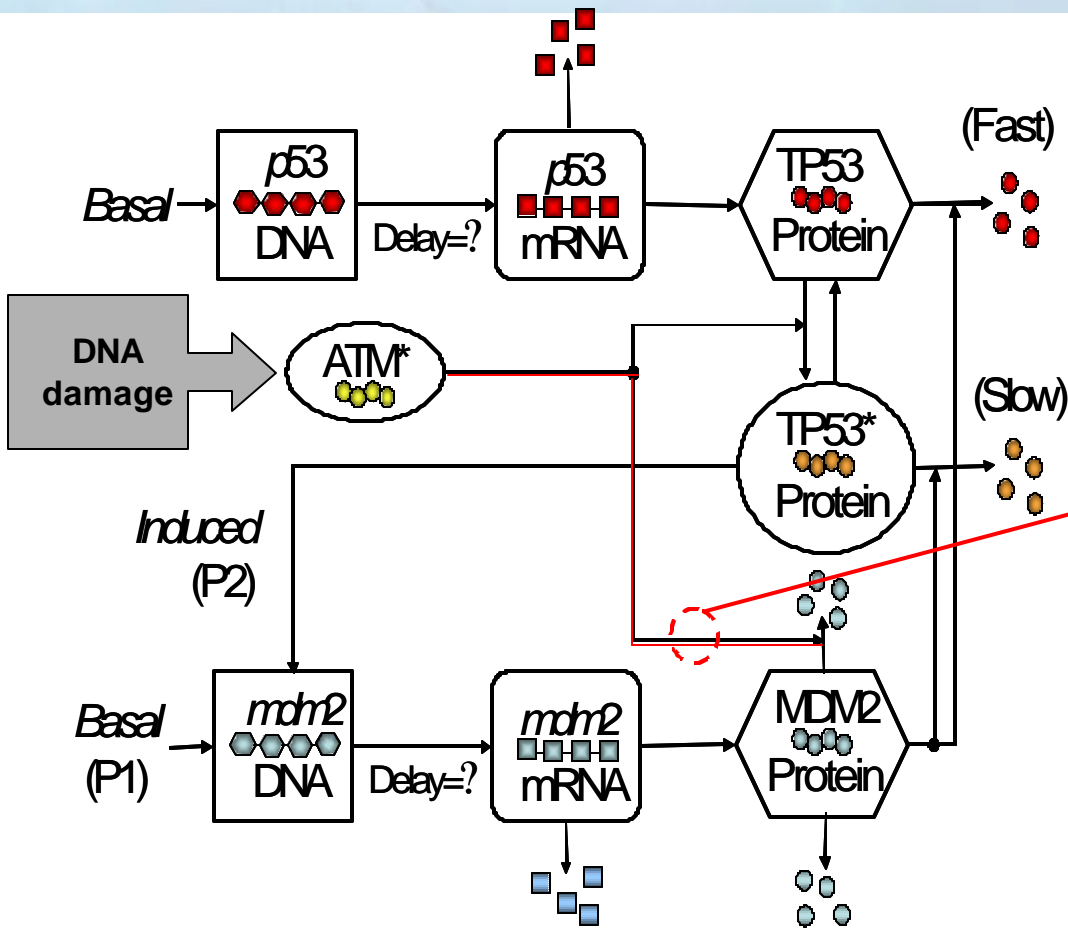
Irradiation



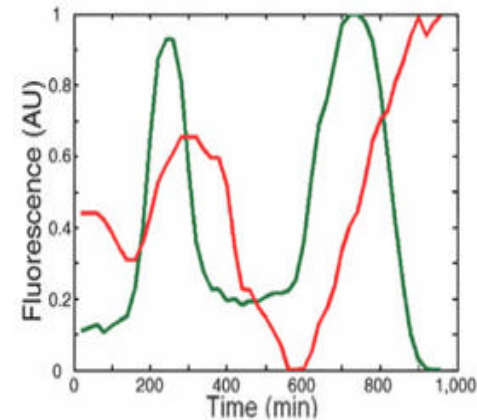
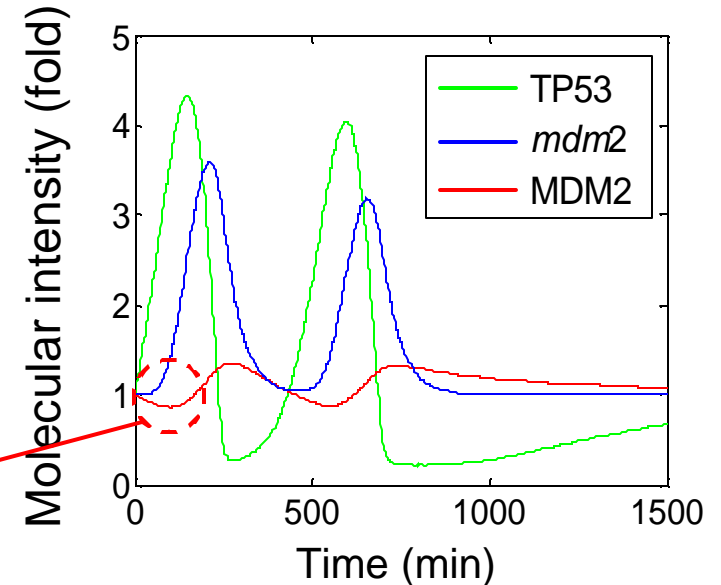
p53 protein



Digital response of tumor suppressor p53 to IR



Response to 5Gy



Ma, Wagner, Rice, Hu, Levine and Stolovitzky, A plausible model for the digital response of p53 to DNA damage, Proc. Natl. Acad. Sci. U S A. 102, 14266 (2005).

Wagner; Ma; Rice; Hu; Levine; Stolovitzky, p53-Mdm2 loop controlled by a balance of its feedback strength and effective dampening using ATM and delayed feedback, IEE PROCEEDINGS SYSTEMS BIOLOGY, 152, 3, 109-118 (2005).

Lahav *et al.*, Nature Genetics 2004

Predictions

Figures 4 and 8 from Ma, Wagner *et al.*,

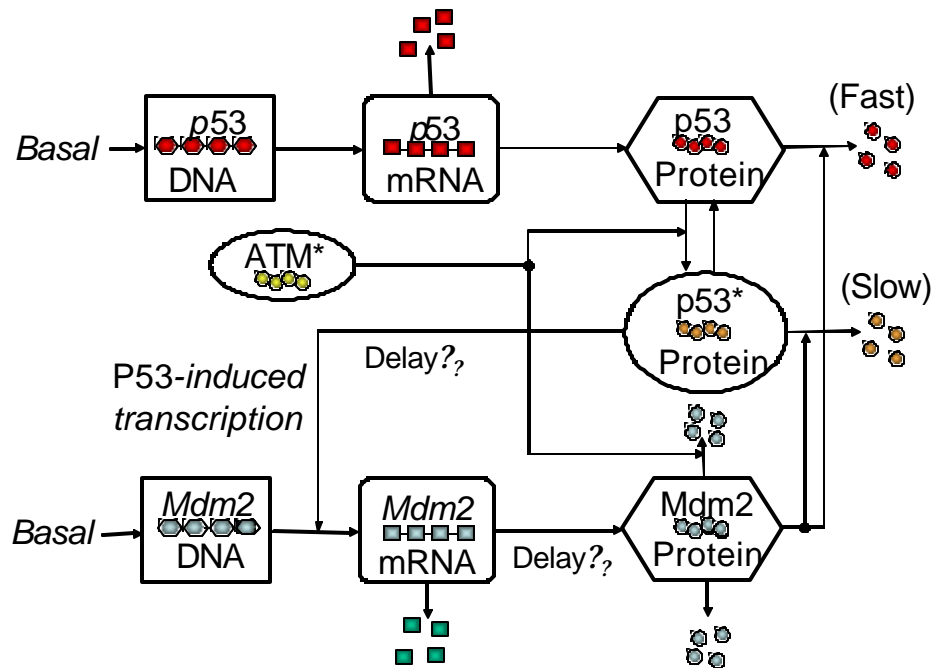
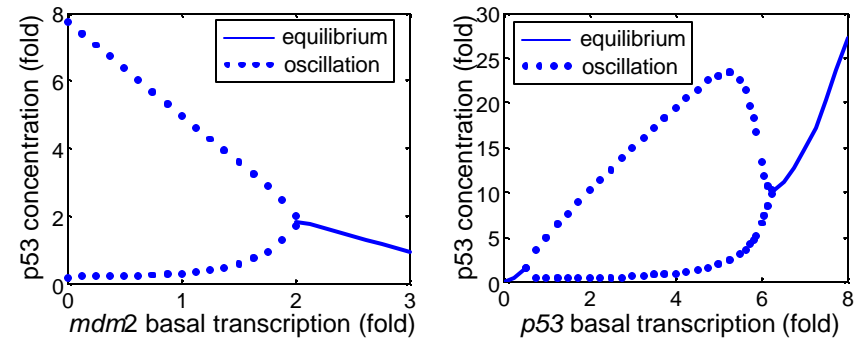


Figure 4 (From Ma, Wagner *et al.*) - Diagram of the p53-Mdm2 oscillator. p53 is translated from *p53* mRNA and inactive for induction of its targets. Phosphorylated by ATM*, p53 becomes active (p53*), and able to transcribe (after a time delay) *Mdm2* which also has a basal transcription rate. Mdm2 protein promotes a fast degradation of p53 and a slow degradation of p53*. In addition to a basal self-degradation, Mdm2 is degraded by a mechanism stimulated by ATM*.

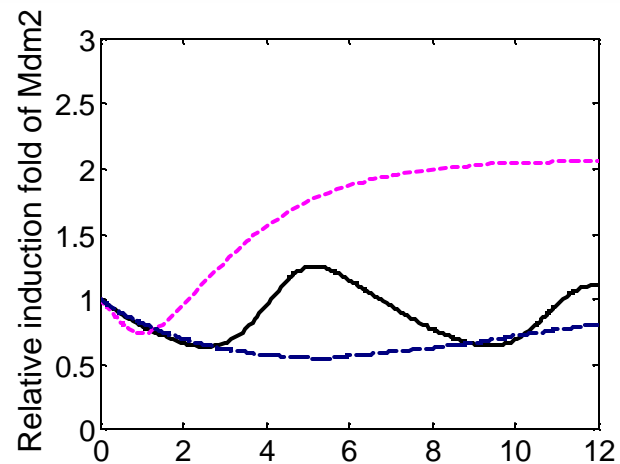
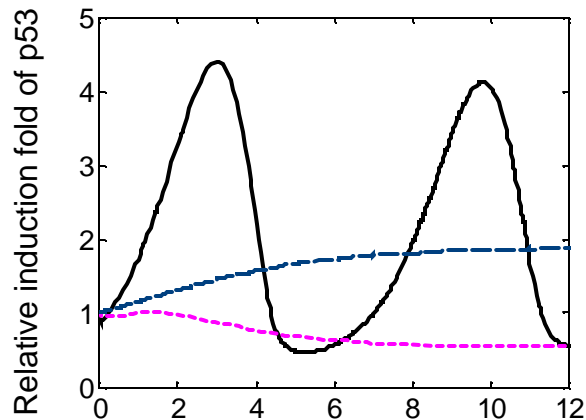
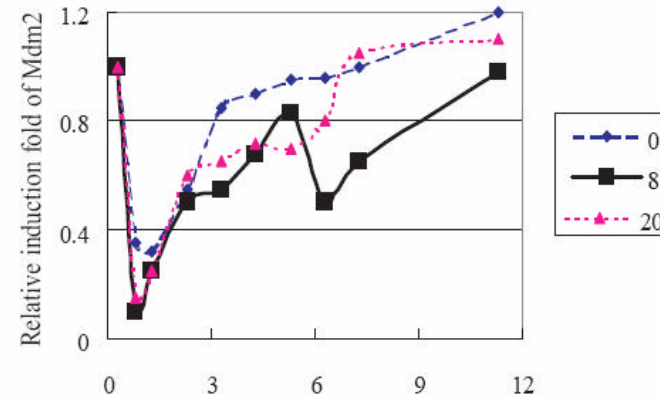
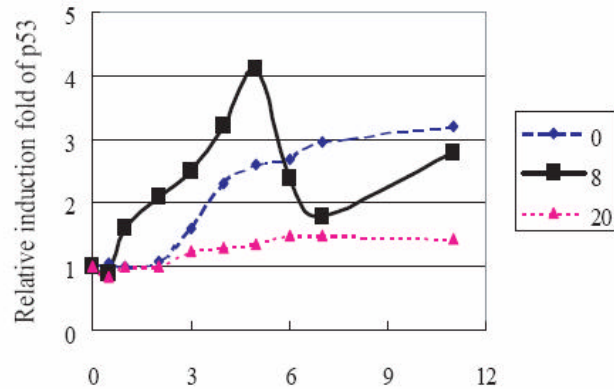


A

B

Figure 8 (From Ma, Wagner, *et al.*) - One-dimensional bifurcation diagrams of steady-state p53 versus single parameter variation of *Mdm2* basal transcription rate (A) or *p53* basal transcription rate (B). The stable equilibrium is represented by solid line. The lower and upper bounds of stable oscillation are represented by paired dotted lines.

Validation of Predictions



Hu, Feng, Ma, Wagner, Rice, Stolovitzky, Levine. “A single nucleotide polymorphism in the MDM2 gene disrupts the oscillation of p53 and MDM2 levels in cells.” *Cancer Res.* 2007 Mar 15;67(6):2757-65.