Computational Modeling of Signaling Pathways Mediating Cell Cycle and Apoptotic Responses to Ionizing Radiation Mediated DNA Damage

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Introduction & Motivation

- Demonstration of the use of a computational systems biology approach to model dose response relationships
- Current biologically motivated dose-response models

  - have only limited reference to the underlying molecular-level mechanisms

  - do not describe how toxicants preturb normal biological function

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Introduction & Motivation

- Integration of computational systems biology approach is the new direction for dose response modeling

  (e.g. *Andersen et al*, *Reproductive Toxicology*, *2005)*

- Advantages and characteristics of this approach

  - multiple level description of biological organization

  - use of sophisticated engineering and mathematical methods to gain deep biological insights

  - direct description of toxicology linking to normal biology

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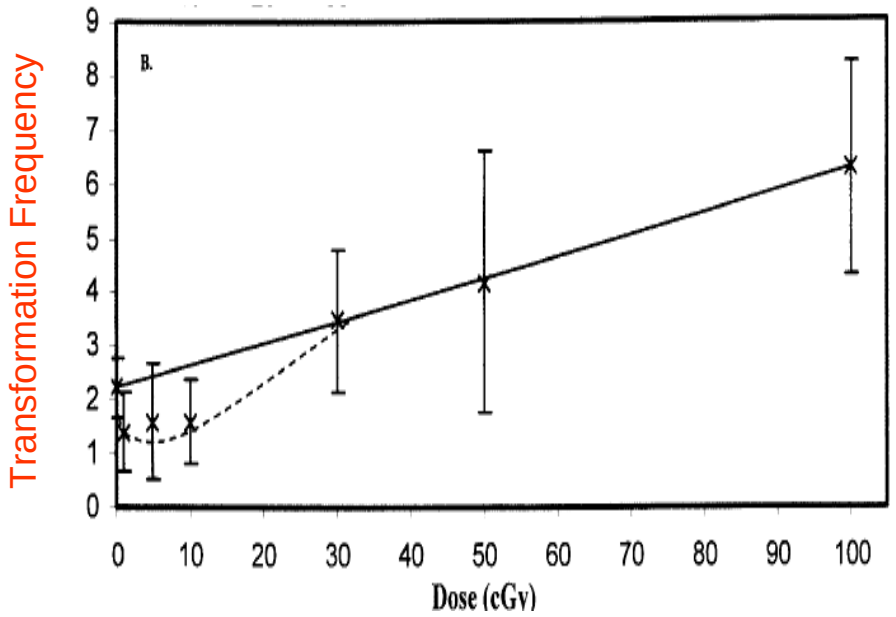
Introduction & Motivation

- For ionizing radiation health risk assessment, linear non-threshold (LNT) model is the default model
- Phenomena such as the adaptive response in the low dose region pose challenges to the LNT model
- Computational systems biology approach is needed



(*Redpath et al, 2001*)

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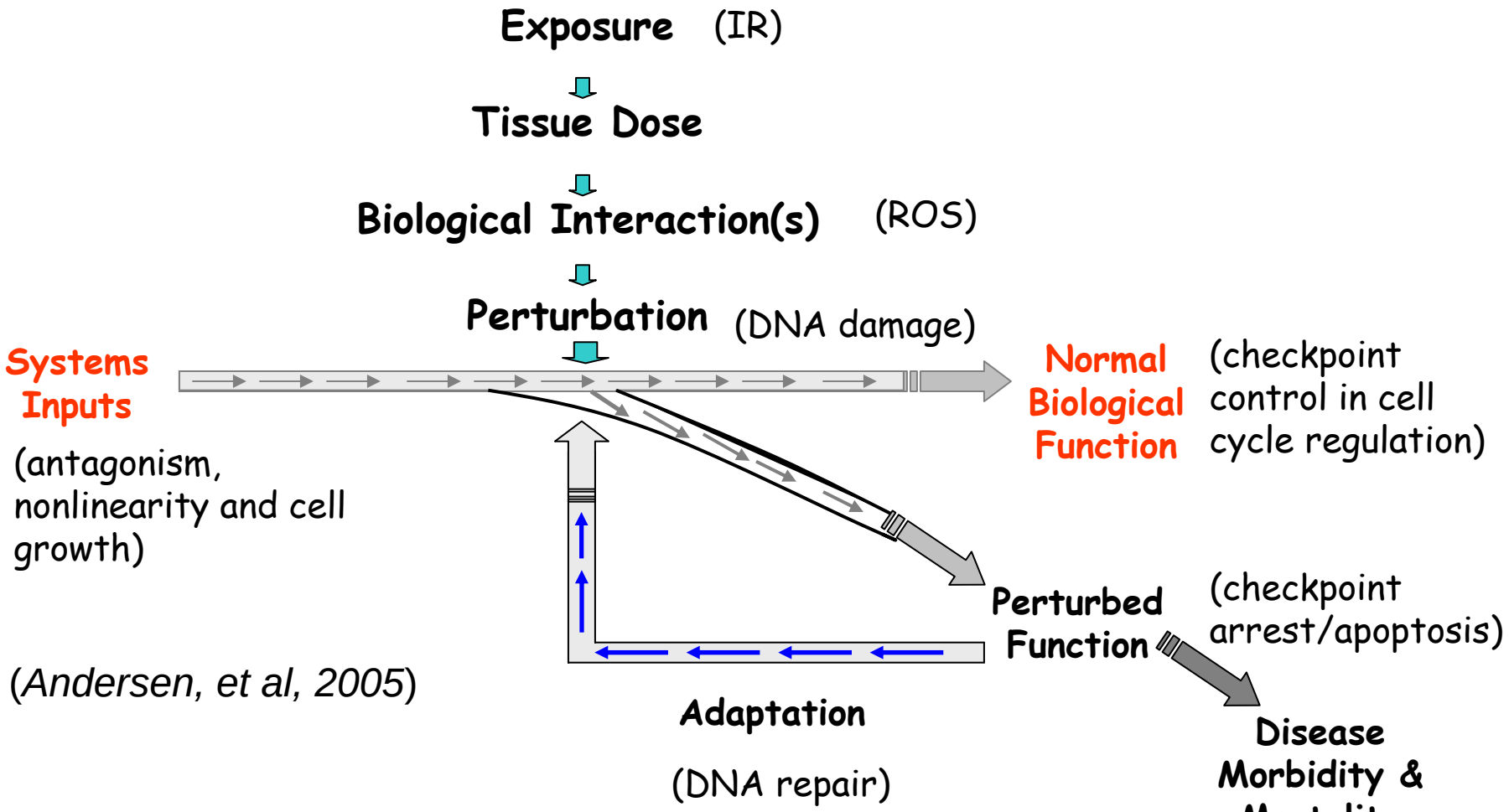
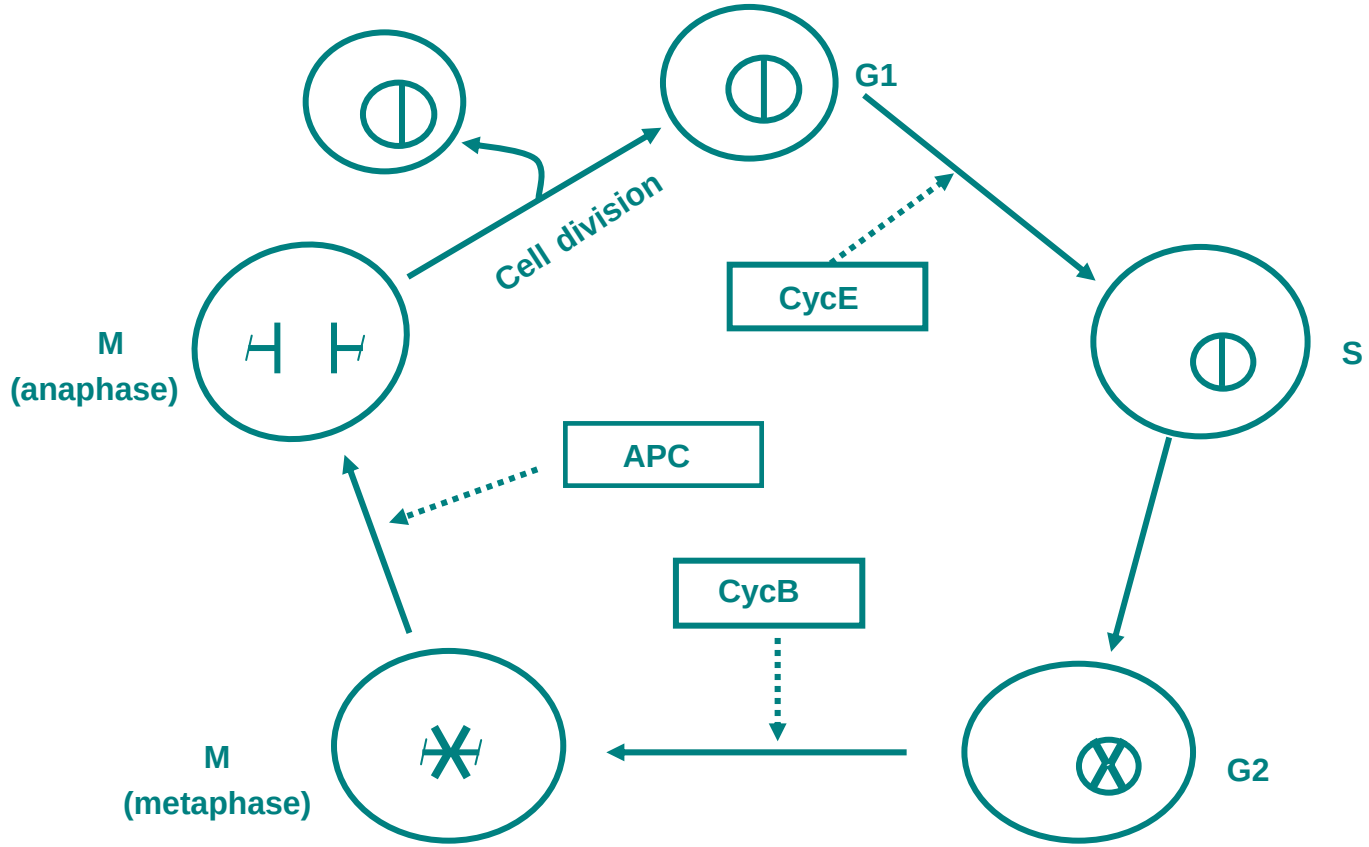
Integration of Computational Systems Biology Approach into Dose Response Modeling

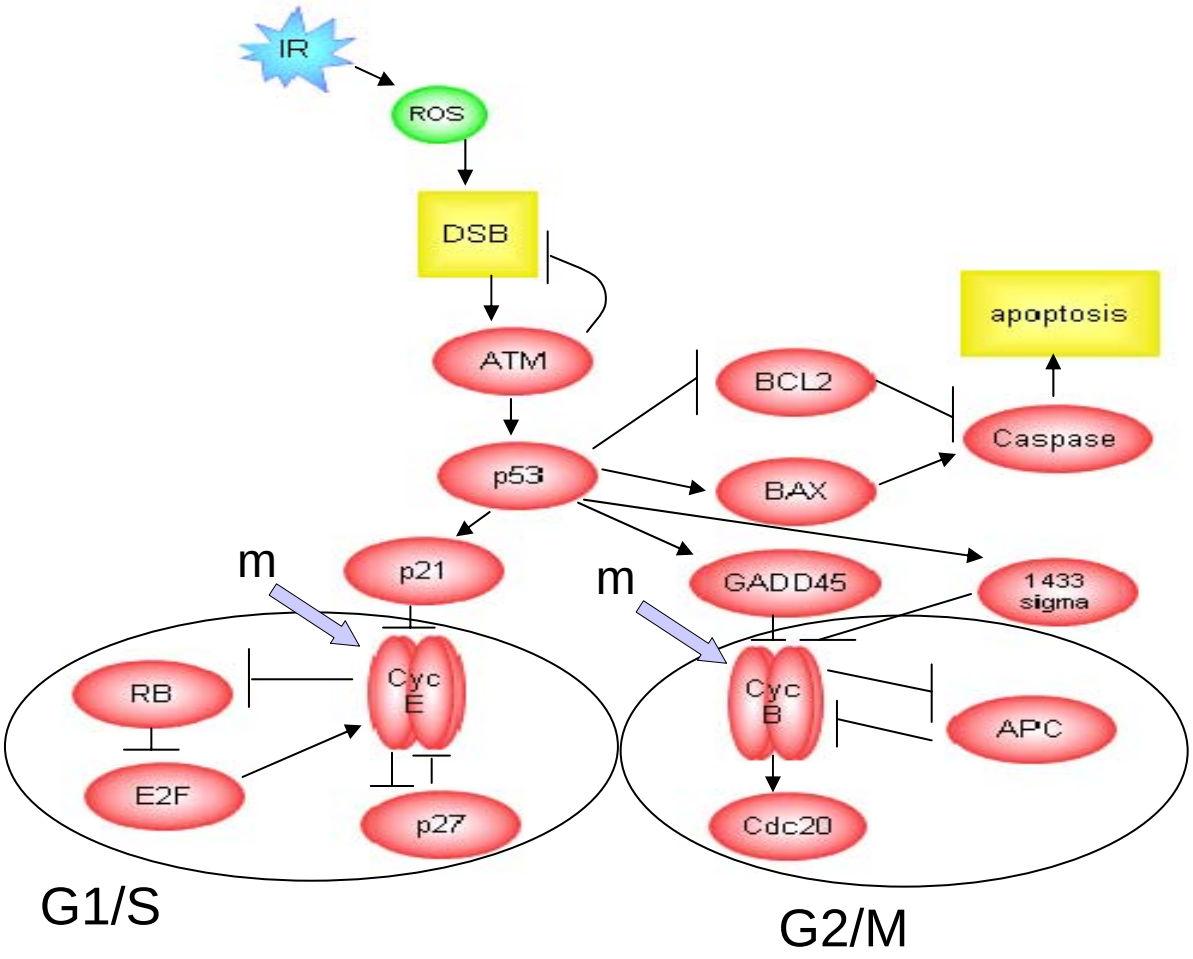


(*Andersen, et al, 2005*)

Incorporate checkpoint control regulation as normal biological function



Checkpoint control regulation and IR-induced perturbation



Mathematical model & parameter assignments

$$\frac{d[CycE]}{dt} = -k_{s1}[p27][CycE] + k_{d1}[p27CycE] - k_{s2}[p27^{p}][CycE] + k_{d2}[p27^{p}CycE] + k_{s3}[E2F] - k_{d3}[CycE] - k_{s4}[CycE][p21] + k_{d4}[CycEp21] \quad (1)$$

$$\frac{d[E2F]}{dt} = -k_{s5}[Rb][E2F] + k_{d5}[RbE2F] - k_{s6}[Rb^{p}][E2F] + k_{d6}[Rb^{p}E2F] \quad (2)$$

$$\frac{d[Rb]}{dt} = -k_{s5}[Rb][E2F] + k_{d5}[RbE2F] - \frac{k_{c1}m[CycE][Rb]}{[Rb] + \frac{(k_{b1}+k_{c1})}{k_{f1}}} + \frac{k_{c2}[EN8][Rb^{p}]}{[Rb^{p}] + \frac{(k_{b2}+k_{c2})}{k_{f2}}} \quad (3)$$

$$\frac{d[Rb^{p}]}{dt} = \frac{k_{c1}m[CycE][Rb]}{[Rb] + \frac{k_{b1}+k_{c1}}{k_{f1}}} - \frac{k_{c2}[EN8][Rb^{p}]}{[Rb^{p}] + \frac{k_{b2}+k_{c2}}{k_{f2}}} - k_{s6}[Rb^{p}][E2F] + k_{d6}[Rb^{p}E2F] \quad (4)$$

$$\vdots$$

$$\frac{dm}{dt} = \mu * m * (1 - m / m_{\max}) \quad (45)$$

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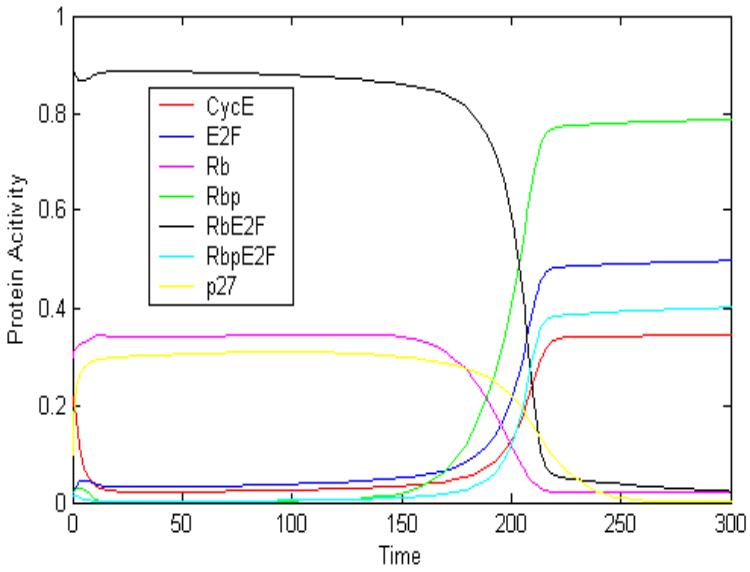
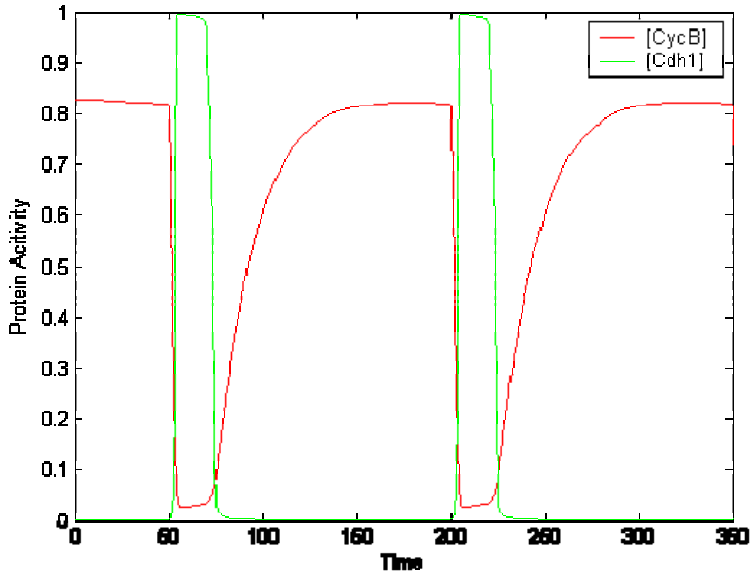
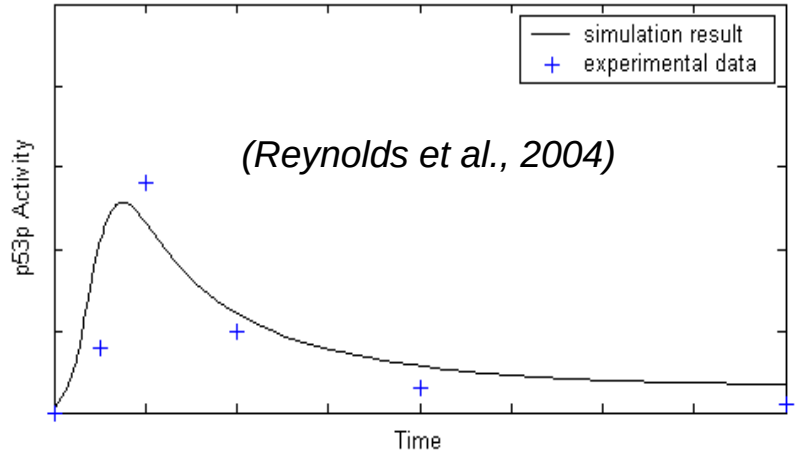
Model verification - switch-like behavior

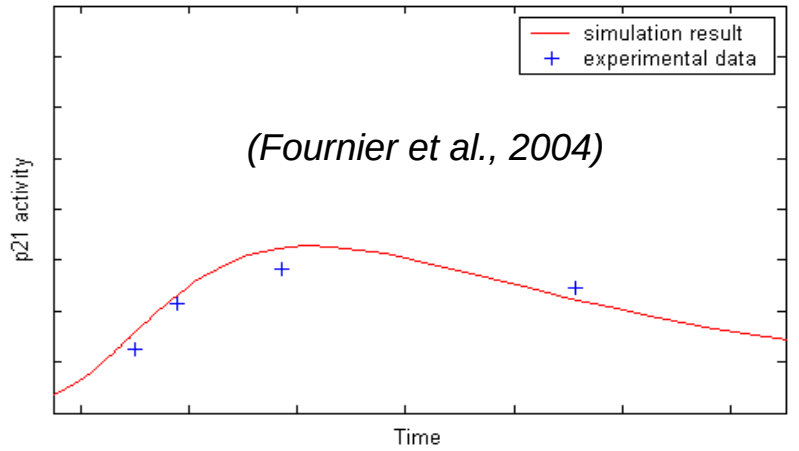


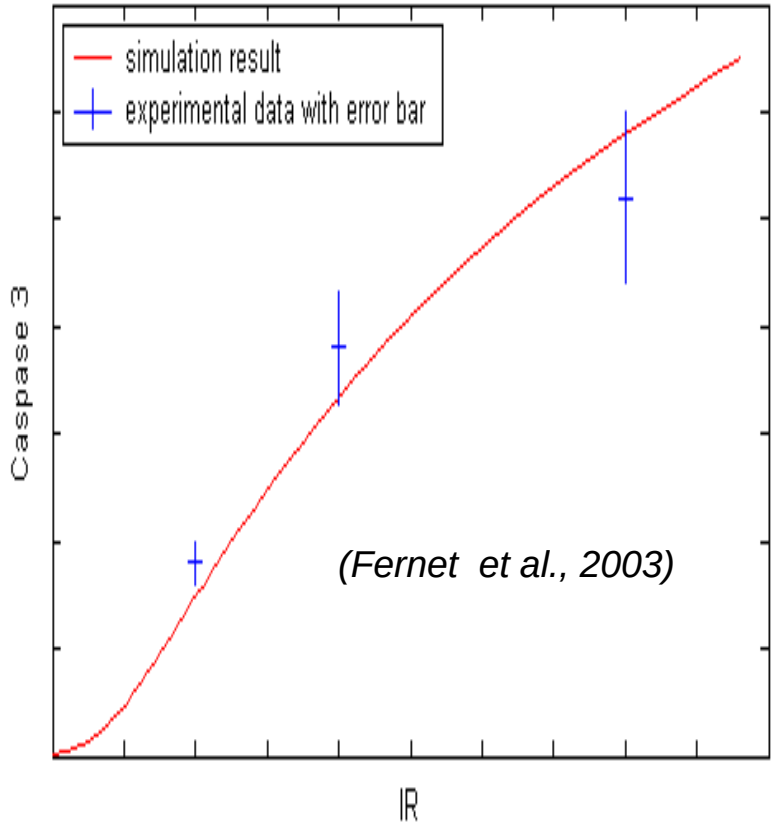


IR = 0

Model verification – comparison with post IR experimental data







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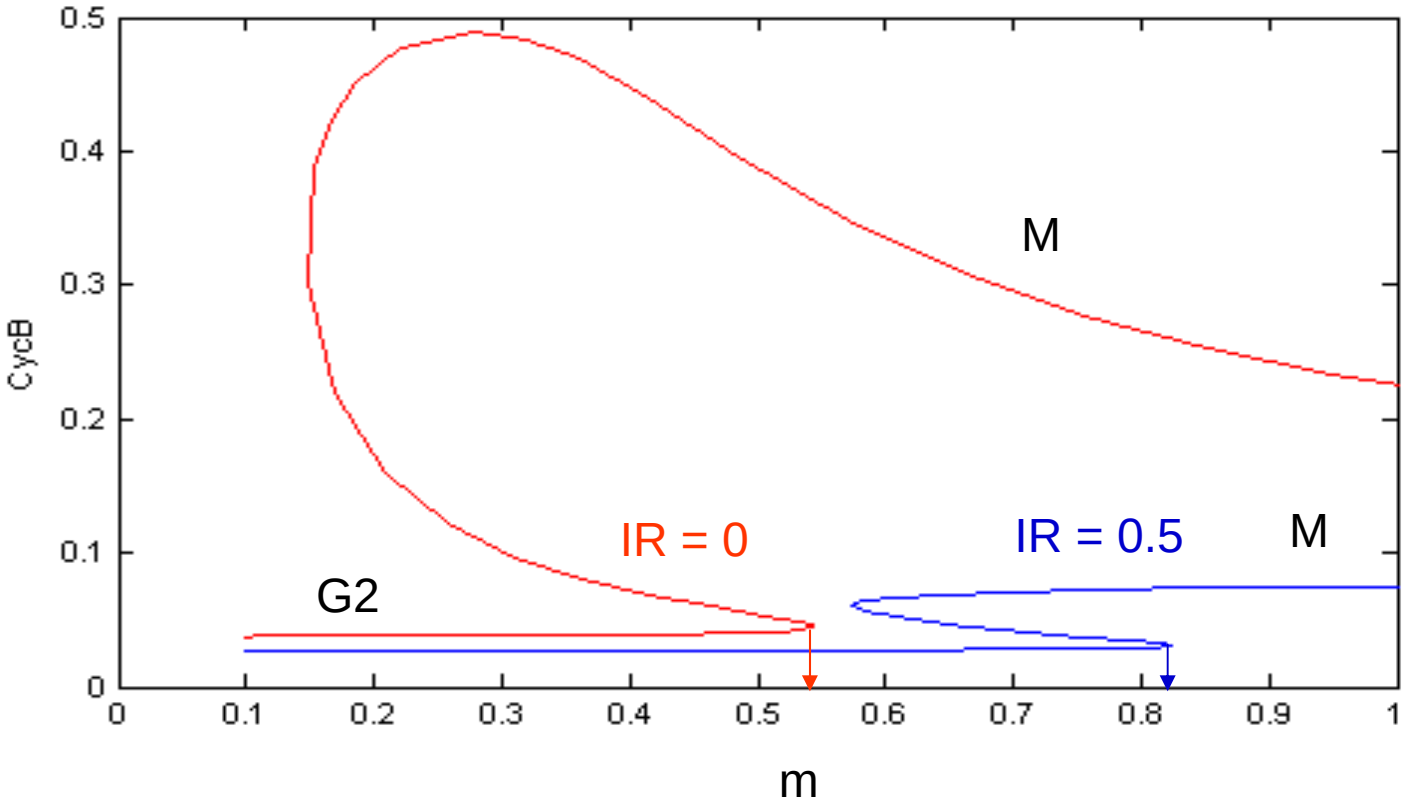
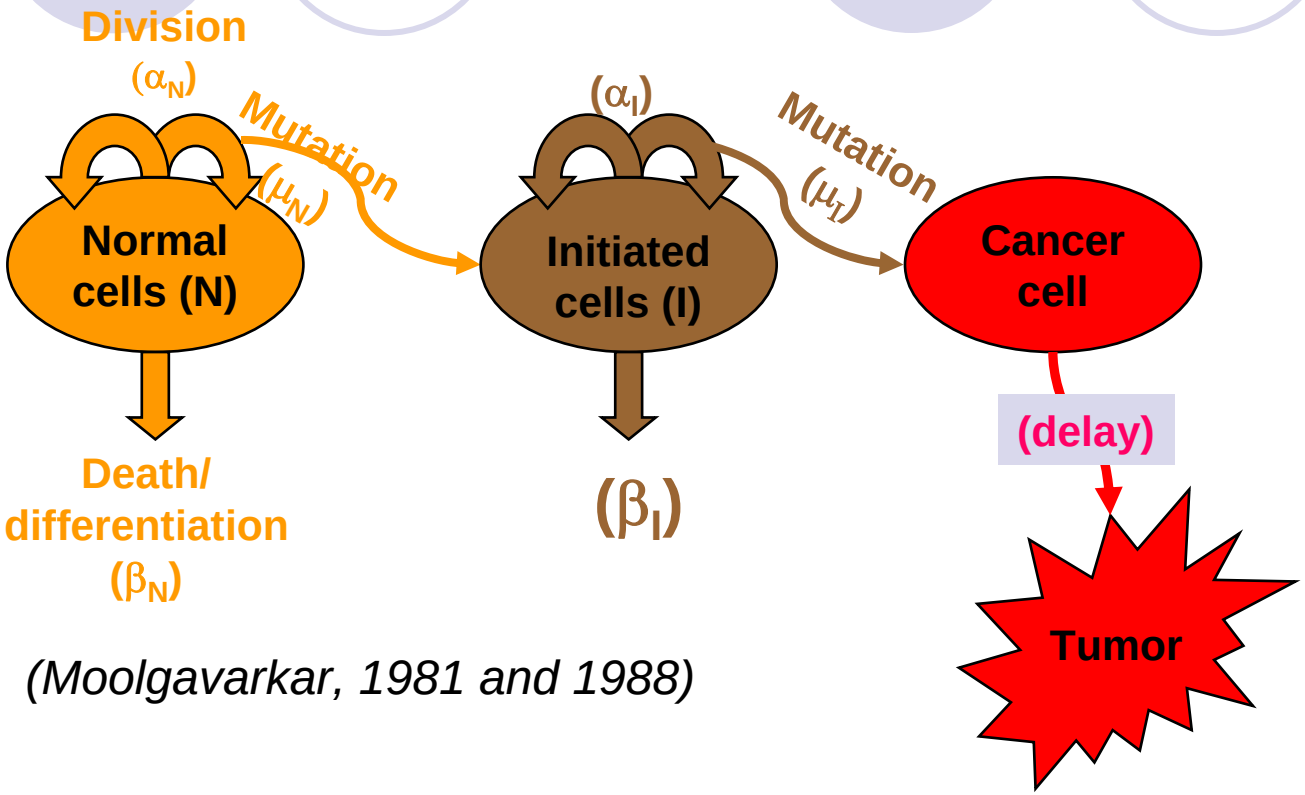
Model verification - checkpoint arrest in G2/M identified by bifurcation diagram



Two-stage clonal growth model

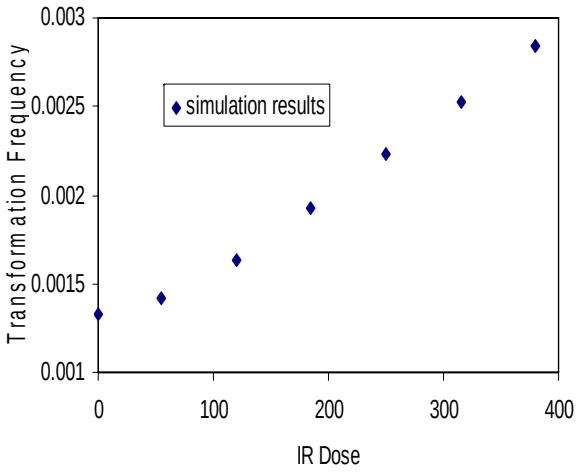


(Moolgavarkar, 1981 and 1988)

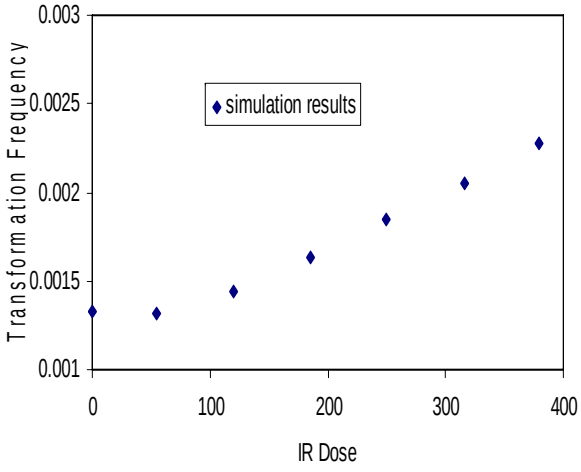
$\partial_N \mu_N$ = *mutational rate (time^{-1}), taken as surrogate for transformation frequency*

Model prediction of dose response – transformation frequency vs. IR

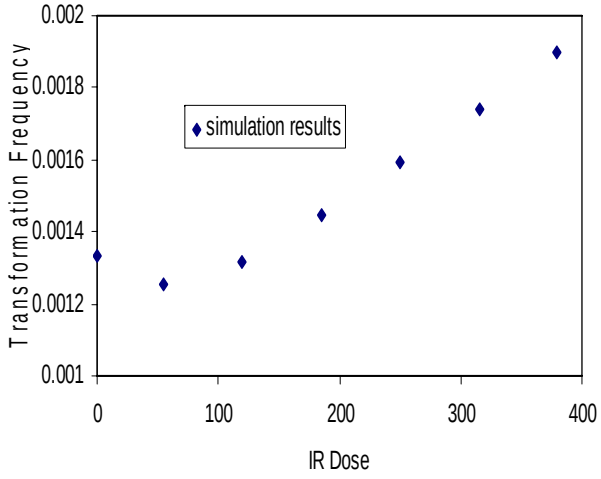
- ∂_N is inverse of cell cycle time
- $\mu_N = \mu_{bas} + k \bullet IR$ μ_{bas} = 0.01
- 3 cases are evaluated $k = 5.3, 3.7, 2.7 \times 10^{-5}$
- monotonical, non-monotonical, J-shaped results



Case 1

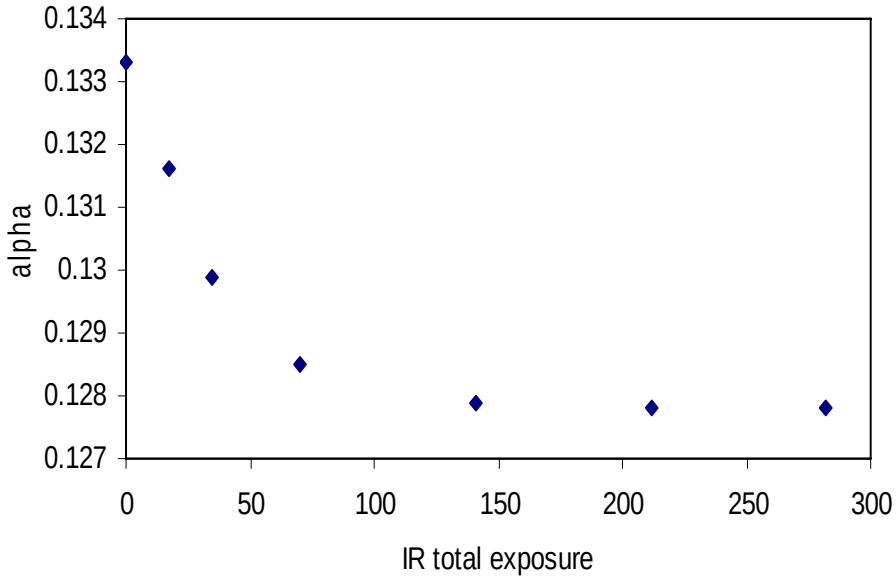


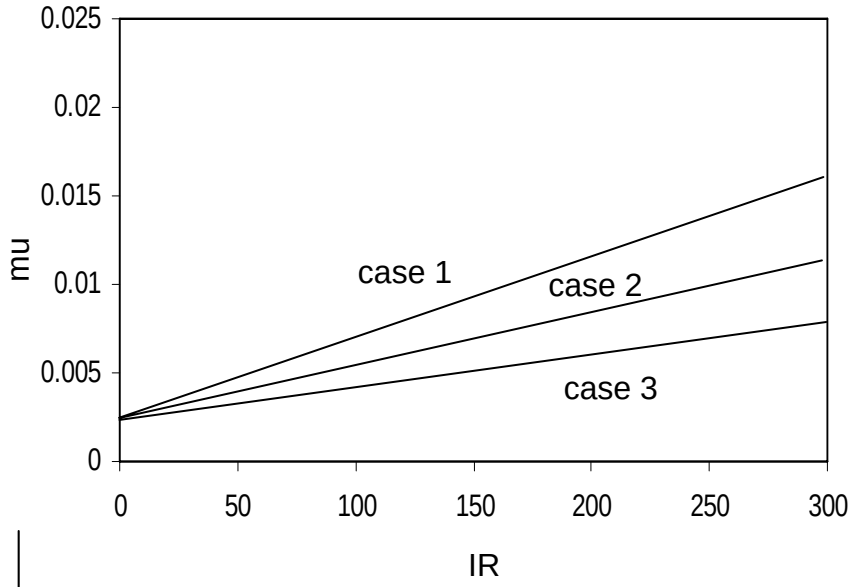
Case 2



Case 3

Why does J-shaped curve happen?





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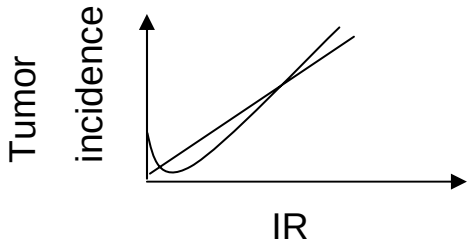

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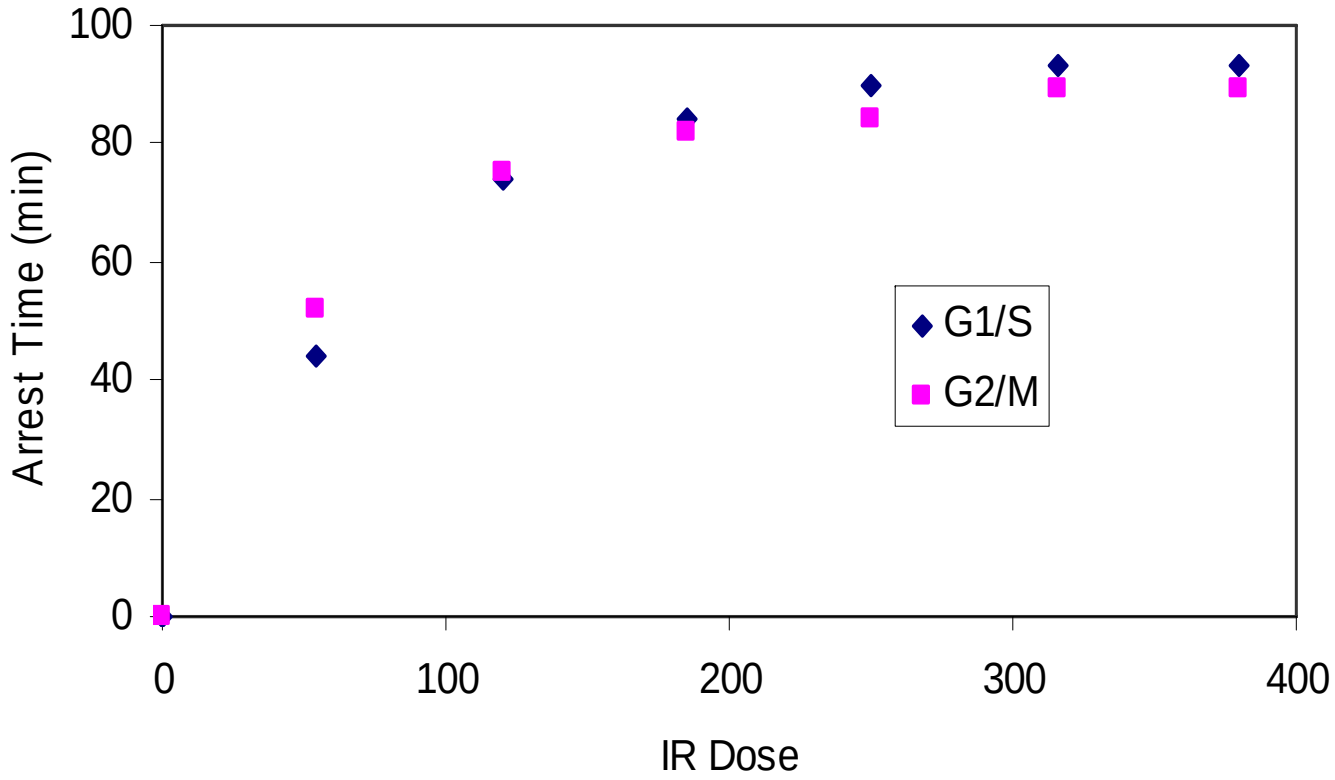

Conclusions, Technical Challenges and Recommendations

- Computational systems biology approach integrates lower level biological mechanisms into dose response model and provides a direct linkage between “toxicology” and “biology”
- Mathematical method assists to explore the underlying biological mechanisms
- More data from the same cell line is needed to make the model fully quantitative
- Apoptosis should be included into dose response model
- Sensitivity study to identify the appropriate parameter ranges
- Recommendation of using this approach in risk assessment as a long term goal

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