In analyzing the complex dynamics of biochemical pathways

by

Thanneer Malai Perumal[‡,*] & Rudiyanto Gunawan[‡,†]

Dynamical Bio Systems Laboratory

[‡]Department of Chemical and Biomolecular Engineering,

[†]Bioinformatics Programme,

National University of Singapore

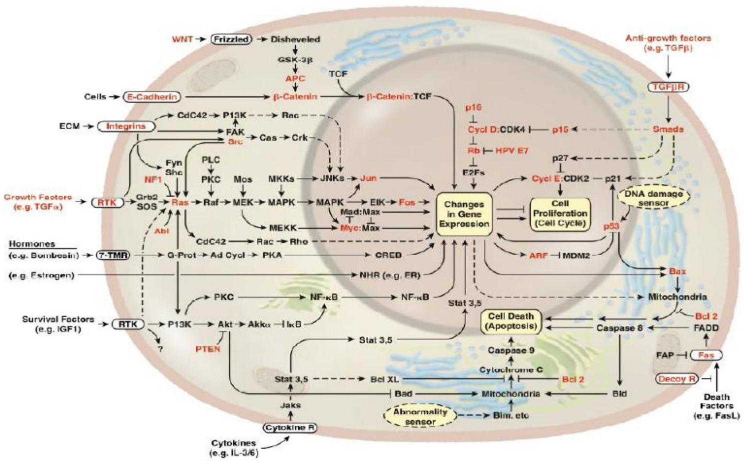
*thanneer@nus.edu.sg

Agenda

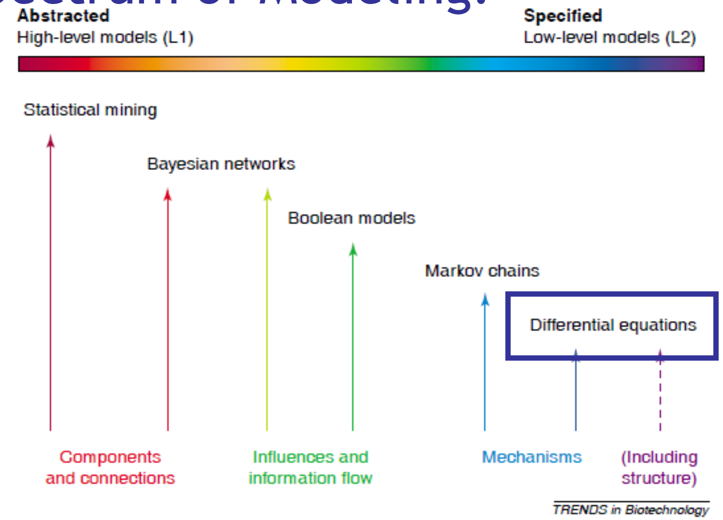
- Biochemical Pathways
- Classical Parametric Sensitivity Analysis (cPSA)
- Caveats of cPSA
- Modified Parametric Sensitivity Analysis (mPSA)
- Case Study: Fas-induced Apoptosis of Human Jurkat T-cell Lines
- Conclusion

Biochemical Pathway Modeling

- Biochemical Pathway:



- Spectrum of Modeling:



- ODE Modeling:

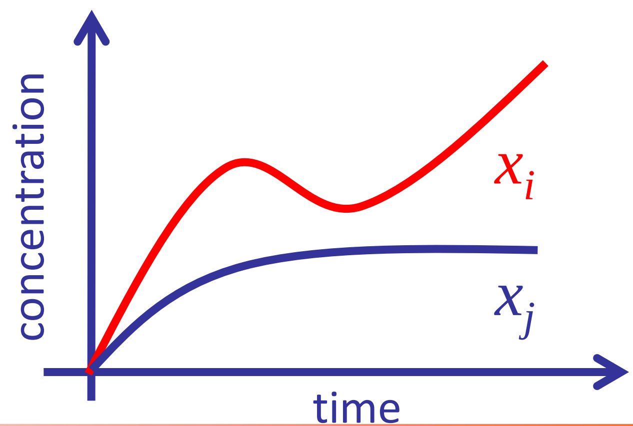
$$\frac{d\mathbf{x}(t,\mathbf{p})}{dt} = f(\mathbf{x},\mathbf{p});\ \mathbf{x}(t_0) = \mathbf{x}_0$$

where

$$\mathbf{x} \in \mathrm{R}^n \quad and \quad \mathbf{x}_0 \in \mathrm{R}^n$$

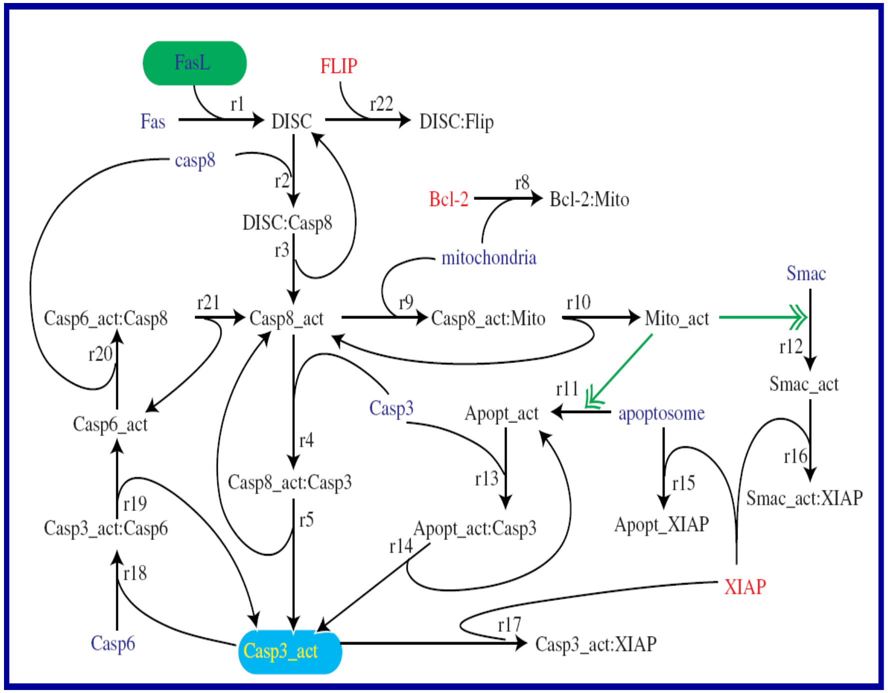
$$\mathbf{p} \in \mathrm{R}^m$$

- State Profiles:



Alberts,B. et al., (2002), *Mol. Biol. of the cell*
Ideker,T., et al., (2003), *Trends in Biotech.*, 21 (6) pp.255

Classical Parametric Sensitivity Analysis



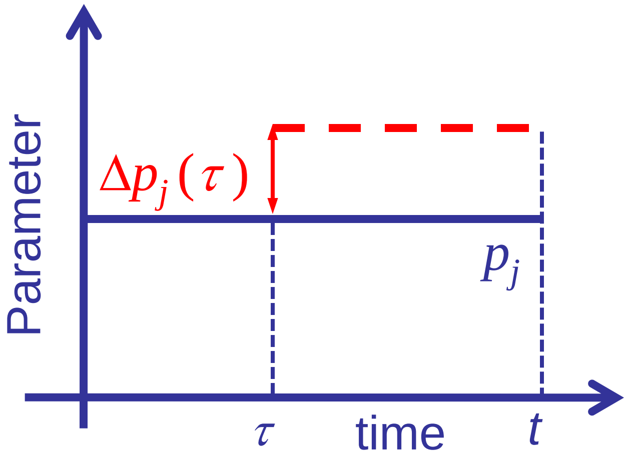
$$\frac{d\mathbf{x}(t,\mathbf{p})}{dt} = f(\mathbf{x},\mathbf{p});\ \ \mathbf{x}(\tau) = \mathbf{x}_0$$

$$\frac{d}{dt}\frac{d\mathbf{x}}{d\mathbf{p}} = \frac{\partial f}{\partial \mathbf{x}}\frac{d\mathbf{x}}{d\mathbf{p}} + \frac{\partial f}{\partial \mathbf{p}}\ ;\ \frac{d\mathbf{x}}{d\mathbf{p}}(\tau) = \begin{bmatrix} \mathbf{0}^{n\times m} & \mathbf{I}^{n\times n} \end{bmatrix}$$

$$\mathbf{S}_{\mathbf{classical}} = \frac{d\mathbf{x}}{d\mathbf{p}} = \int_{\tau}^{t} \frac{d}{dt}\frac{d\mathbf{x}}{d\mathbf{p}}\, d\hat{t}$$

$$S_{i,j}^{x}(t,\tau) = \frac{\text{Change in state at any time } t}{\text{Change in parameter at any time } \tau} = \frac{\partial x_i(t)}{\partial p_j(\tau)}$$

Classical Parametric Sensitivity Analysis



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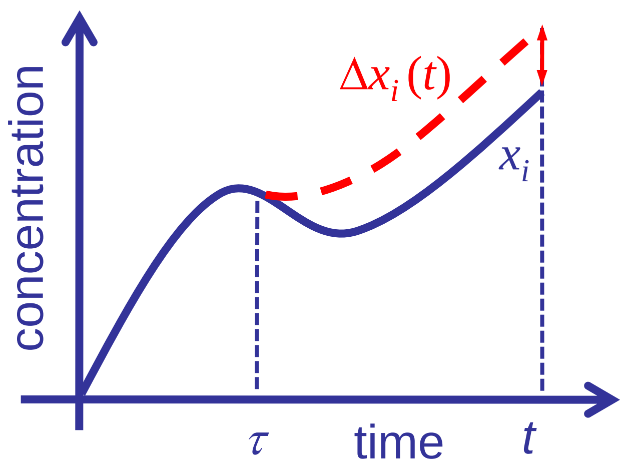

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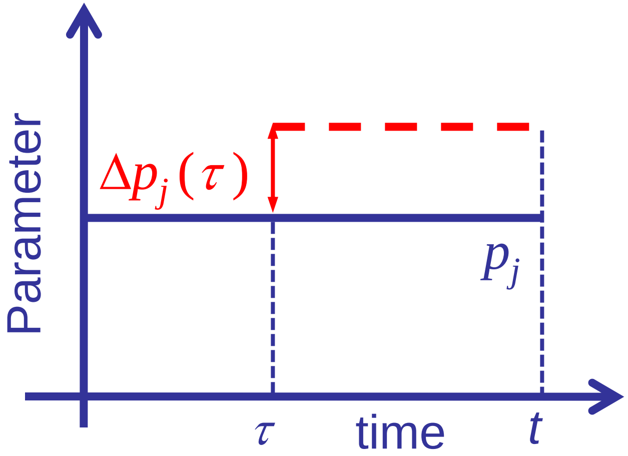
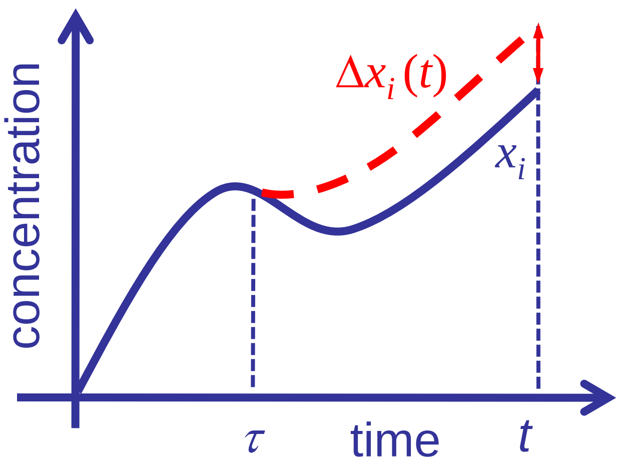
$$S^{x}_{i,j}(t,\tau) = \frac{\text{Change in state at any time } t}{\text{Change in parameter at any time } \tau} = \frac{\partial x_i(t)}{\partial p_j(\tau)}$$

Caveats of cPSA





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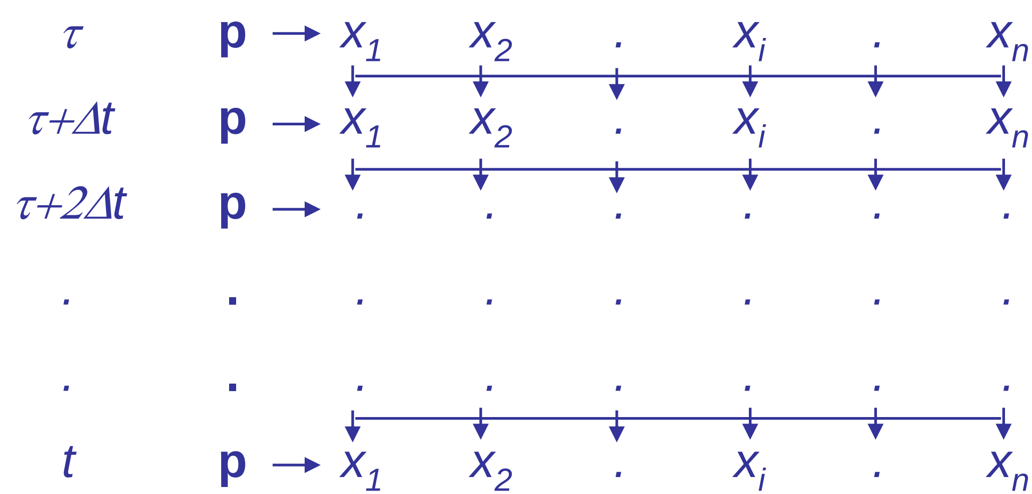
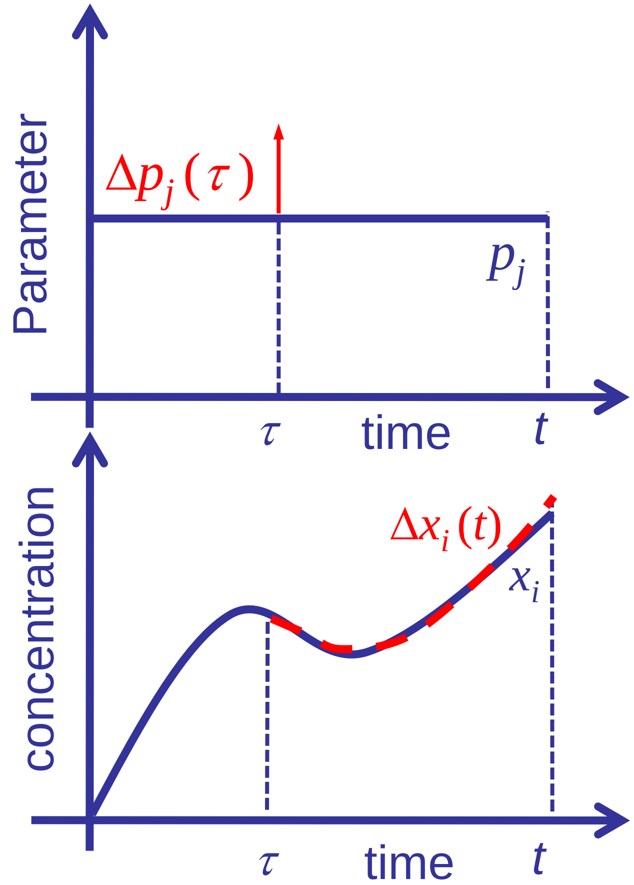


$S_{classical}$ is the effect of integrated perturbations of parameter on the states

Modified Parametric Sensitivity Analysis

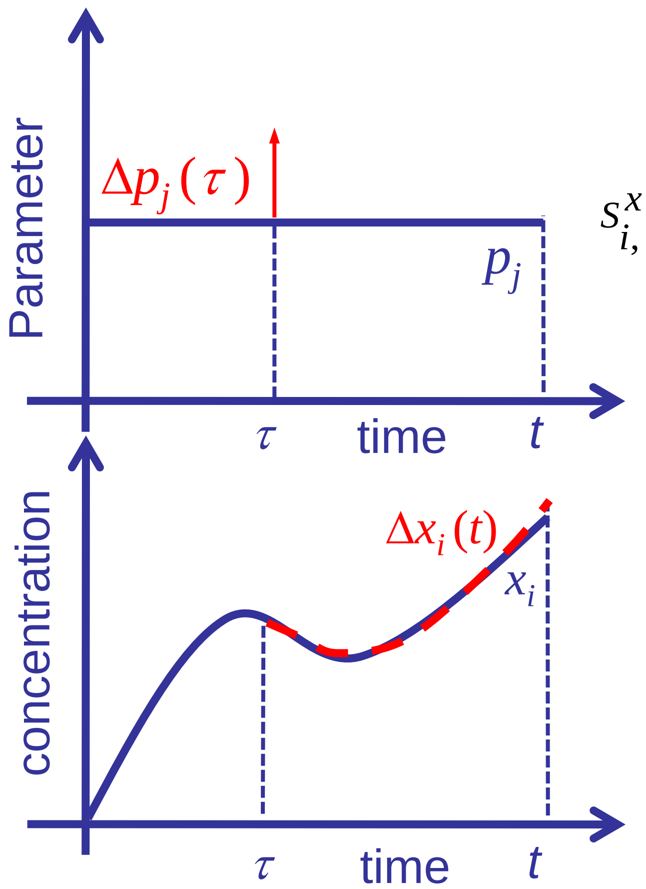


$$\frac{d\mathbf{x}(t,\mathbf{p})}{dt} = f(\mathbf{x},\mathbf{p});\ \mathbf{x}(\tau)=\mathbf{x}_0$$

$$\frac{d}{dt}\frac{d\mathbf{x}}{d\mathbf{p}} = \frac{\partial f}{\partial \mathbf{x}}\frac{d\mathbf{x}}{d\mathbf{p}} + \frac{\partial f}{\partial \mathbf{p}};\ \frac{d\mathbf{x}}{d\mathbf{p}}(\tau) = \begin{bmatrix}\mathbf{0}^{n\times m} & \mathbf{I}^{n\times n}\end{bmatrix}$$

$$S^{x}_{i,j}(t,\tau) = \frac{\text{Effect of impulse change in state at any time } t}{\text{Impulse change in parameter at any time } \tau} = \frac{\partial x_i(t)}{\partial p_j(\tau)} = \frac{\partial f_i(\tau)}{\partial p_j(\tau)}$$

Modified Parametric Sensitivity Analysis

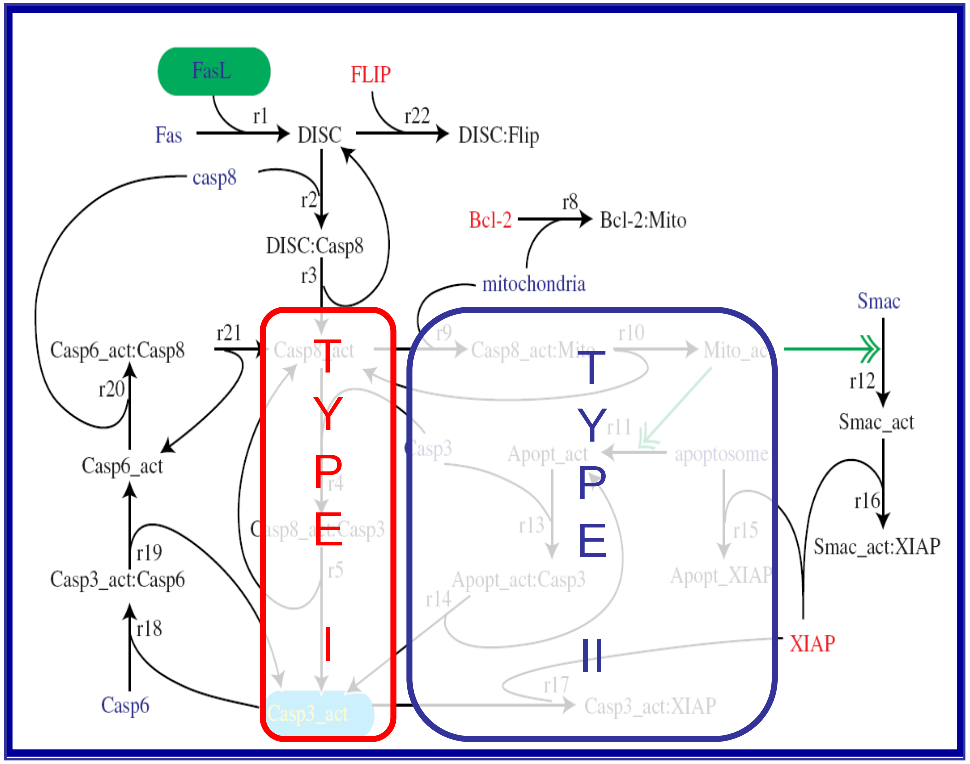


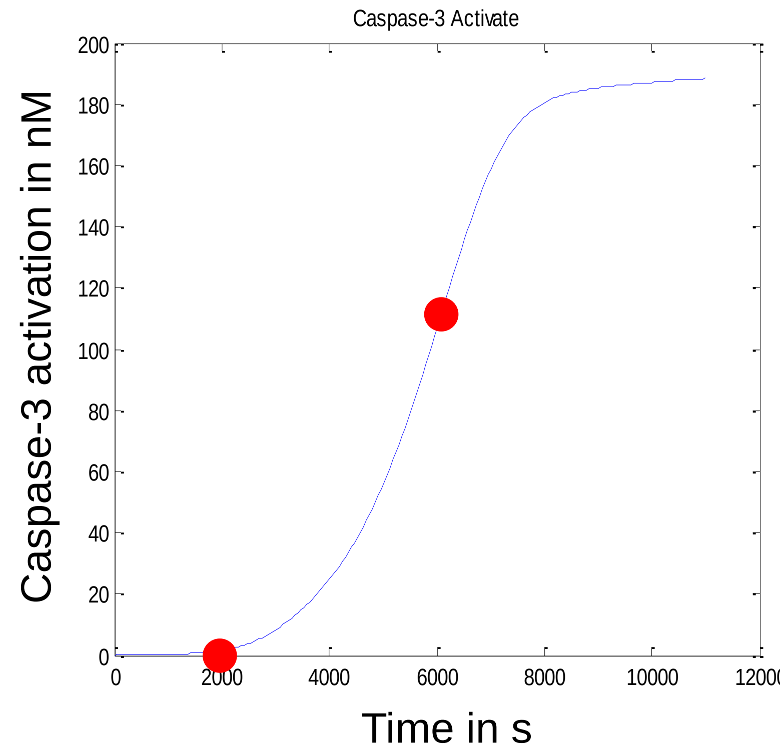
$$S_{i,j}^{x}(t,\tau)=\frac{\text{Effect of impulse change in state at any time } t}{\text{Impulse change in parameter at any time } \tau}=\frac{\partial x_i(t)}{\partial p_j(\tau)}=\frac{\partial f_i(\tau)}{\partial p_j(\tau)}$$

τ	**p** →	x_1	x_2	.	x_i	.	x_n
$\tau+\Delta t$	**p** →	x_1	x_2	.	x_i	.	x_n
$\tau+2\Delta t$	**p** →	.	.	.	.	.	.
.	**.**	.	.	.	.	.	.
.	**.**	.	.	.	.	.	.
t	**p** →	x_1	x_2	.	x_i	.	x_n

$S_{modified}$ is only the direct effect of parametric perturbations on the states

Case Study: Fas-induced Cell Death Model

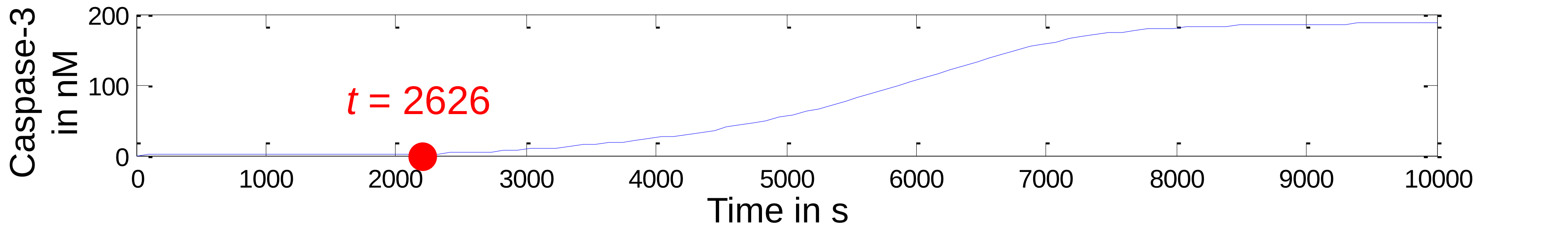


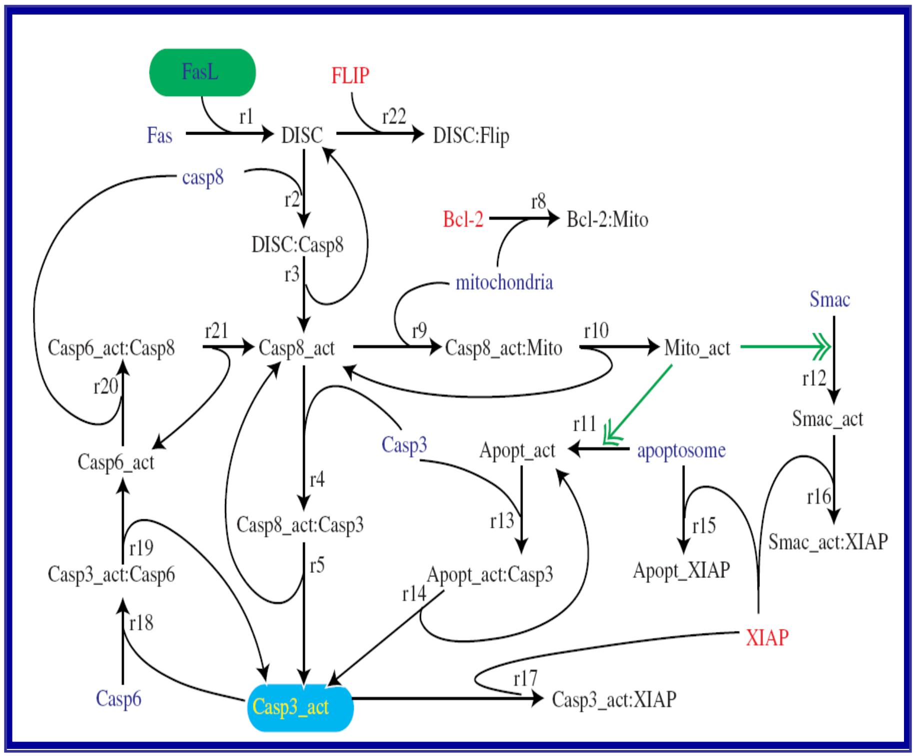


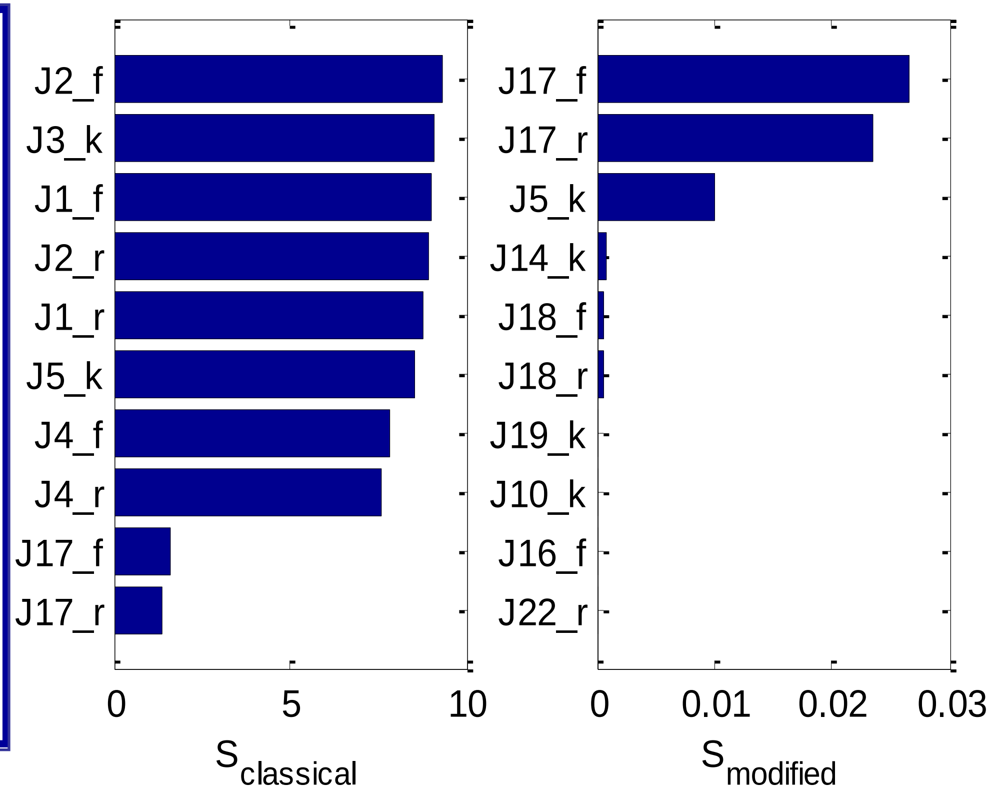
- 29 reacting species
- 22 reactions
- 32 rate constants

Hua F *et al.*, (2006) J R Soc Interface, 515-526

Case Study: Fas-induced Cell Death Model







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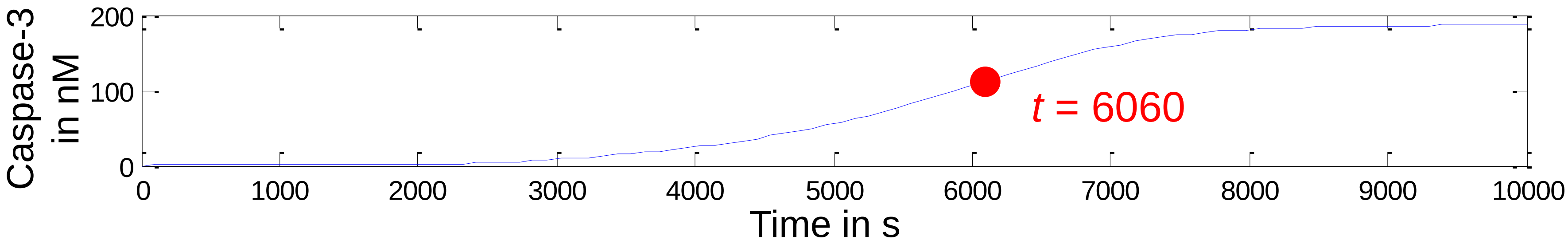
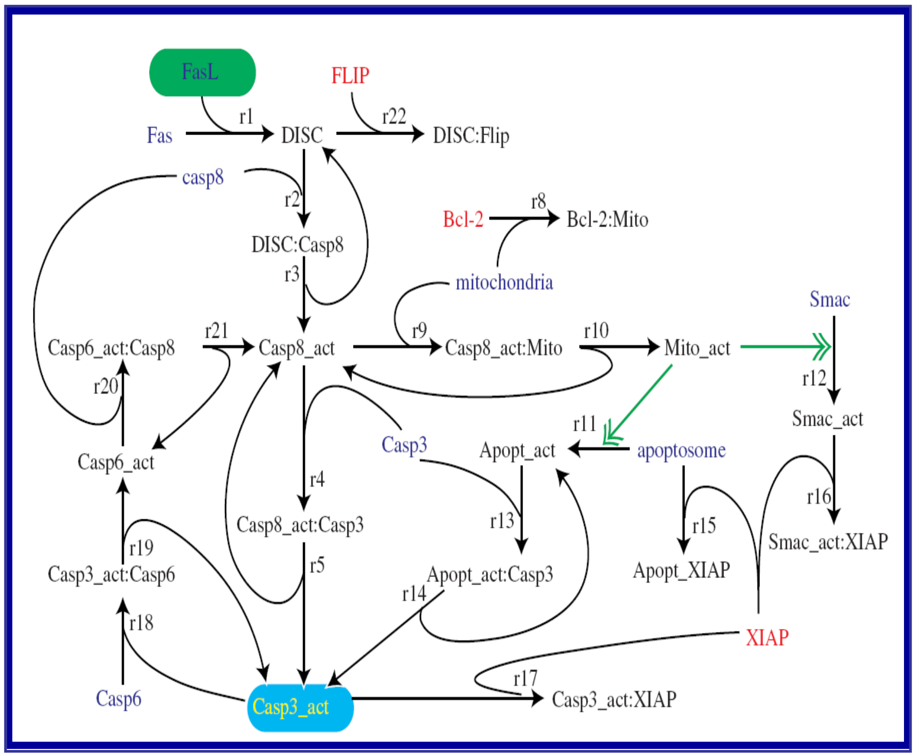
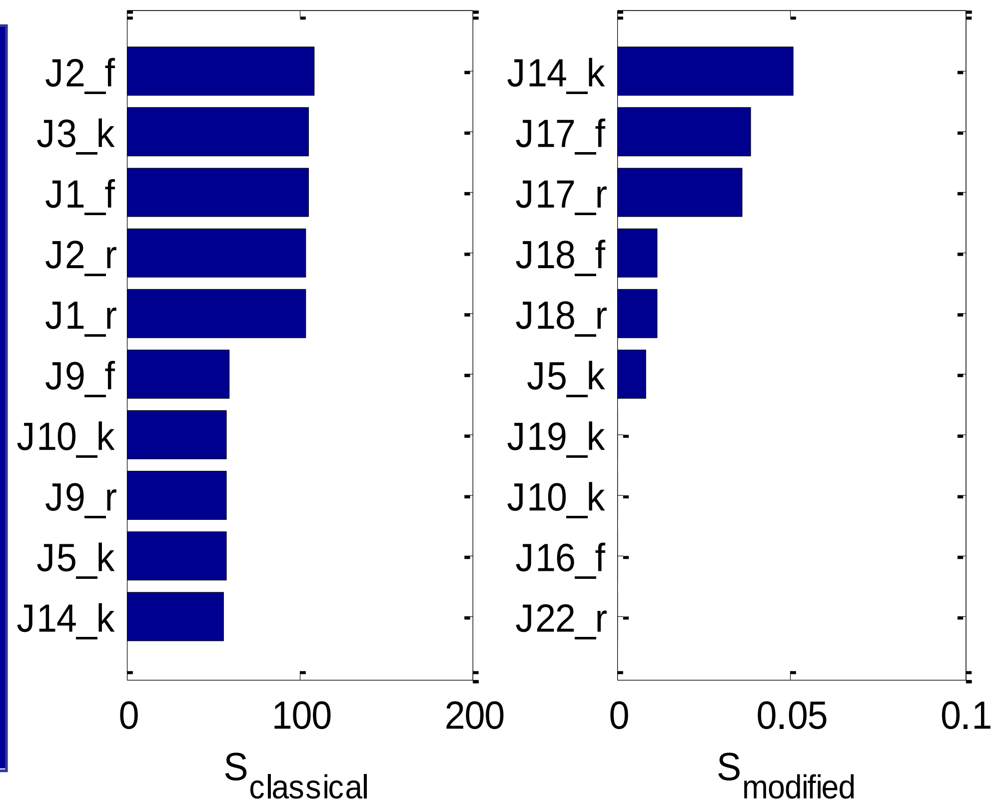
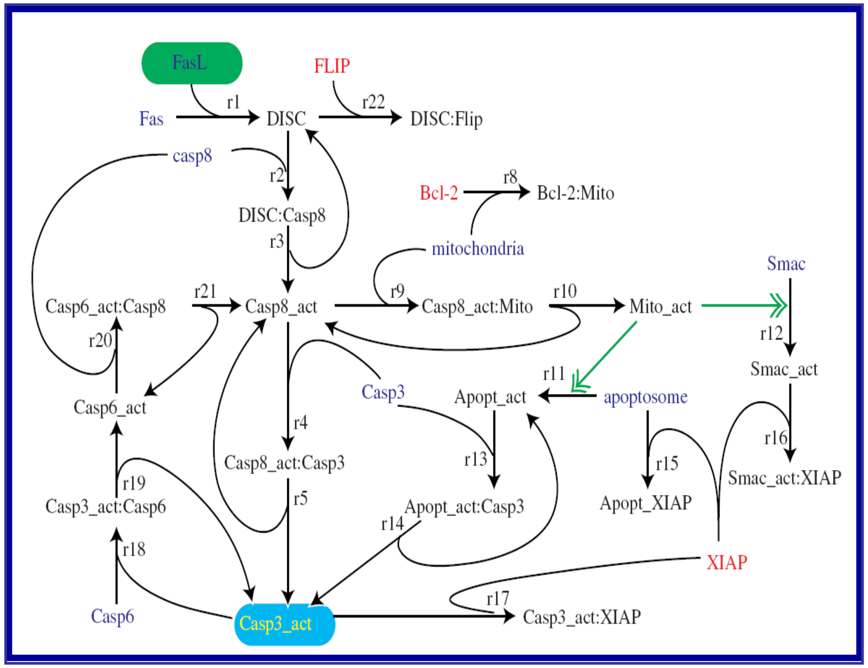
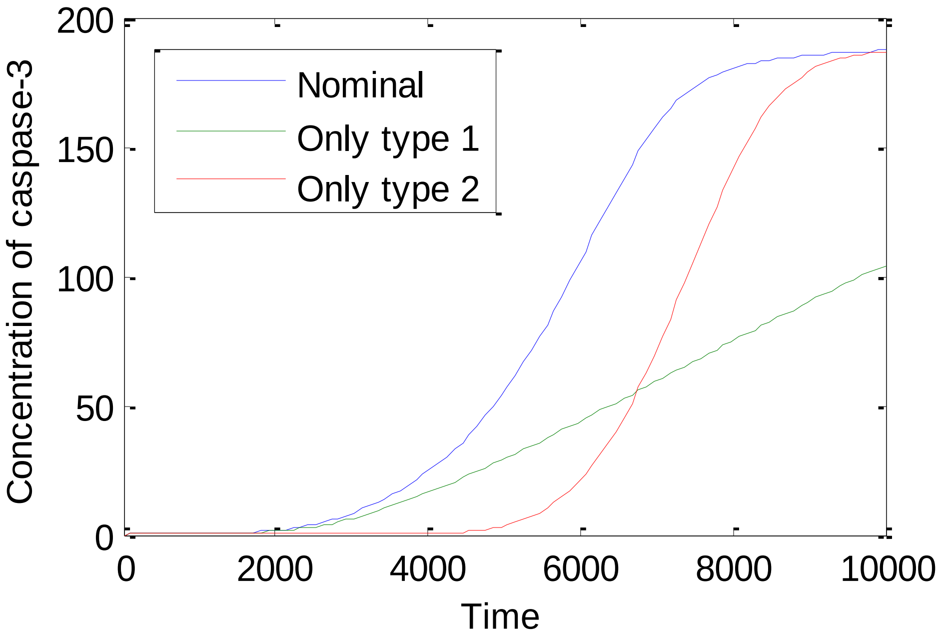






In Silico Validation





- Jurkat cells apoptosis pathway is effected by **type - I** route initially.
- But activation of caspase-3 is majorly **type-II dominant**, which is in agreement with experiments*

*Scaffidi C *et al.*, (1998) EMBO J, 17: 1675-1687

Conclusion

- Mathematical models and their associated quantitative analysis are useful to understand the system dynamics.
- But one should be aware of the nature and type of analysis used and its purpose.
- As shown here, even using standard methods, like classical PSA, can mislead the modeler.
- A modified PSA based on impulse perturbations on system parameters is presented.
- mPSA can offer a step-by-step mechanistic insight on how a particular output behavior is accomplished.

GFM Analysis:

Perumal TM, Wu Y, and Gunawan R. *Dynamical analysis of cellular networks based on the Green's function matrix.* J Theor Biol 2009 Nov 21; 261(2) 248-59. doi:10.1016/j.jtbi.2009.07.037 pmid:19660478.

Acknowledgements

NUS National University of Singapore

Singapore Millennium Foundation Ltd

MINISTRY OF EDUCATION SINGAPORE

NUS National University of Singapore

DYNAMICAL BIO-SYSTEMS LABORATORY
National University of Singapore

Thank You

(thanneer@nus.edu.sg)

Questions?