EGFR model presentation

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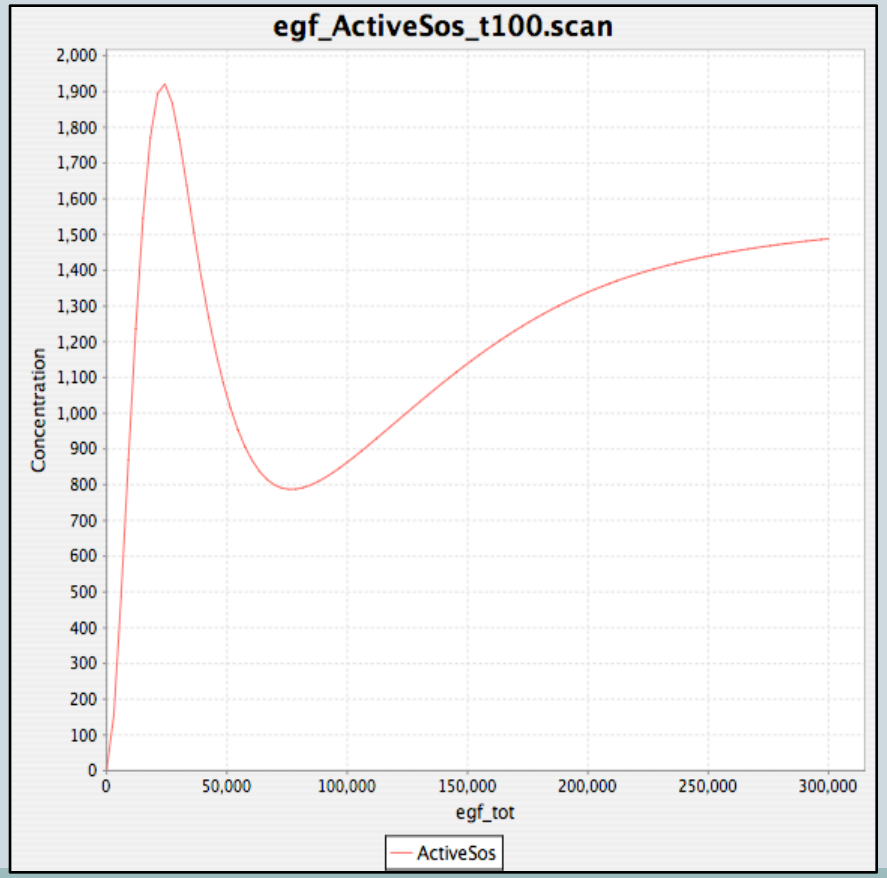
What are we going to talk about?

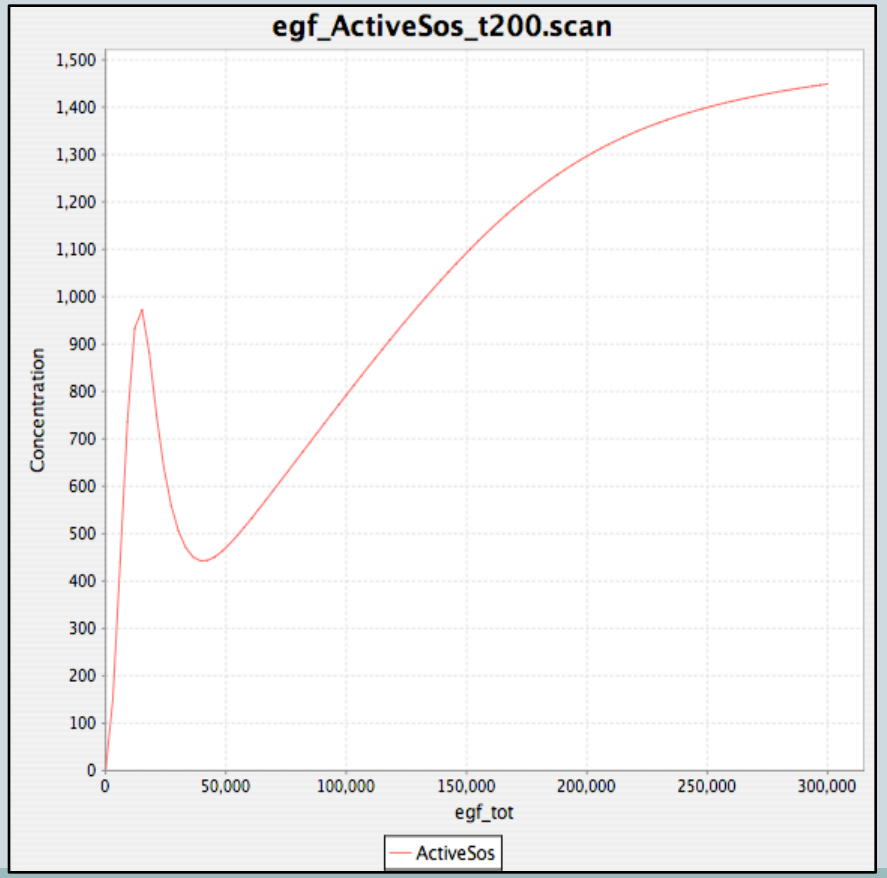
- Phenomena of the Sos-EGF dose response curve (length of run)
- Talking about dimers when rules are for one receptor only
- Splitting the phenomena into cases based on receptor activation

The effect of stimulation on Sos activation: Parameter scan of EGF (ligand) concentration

Total Sos activation against dose
Time = 100

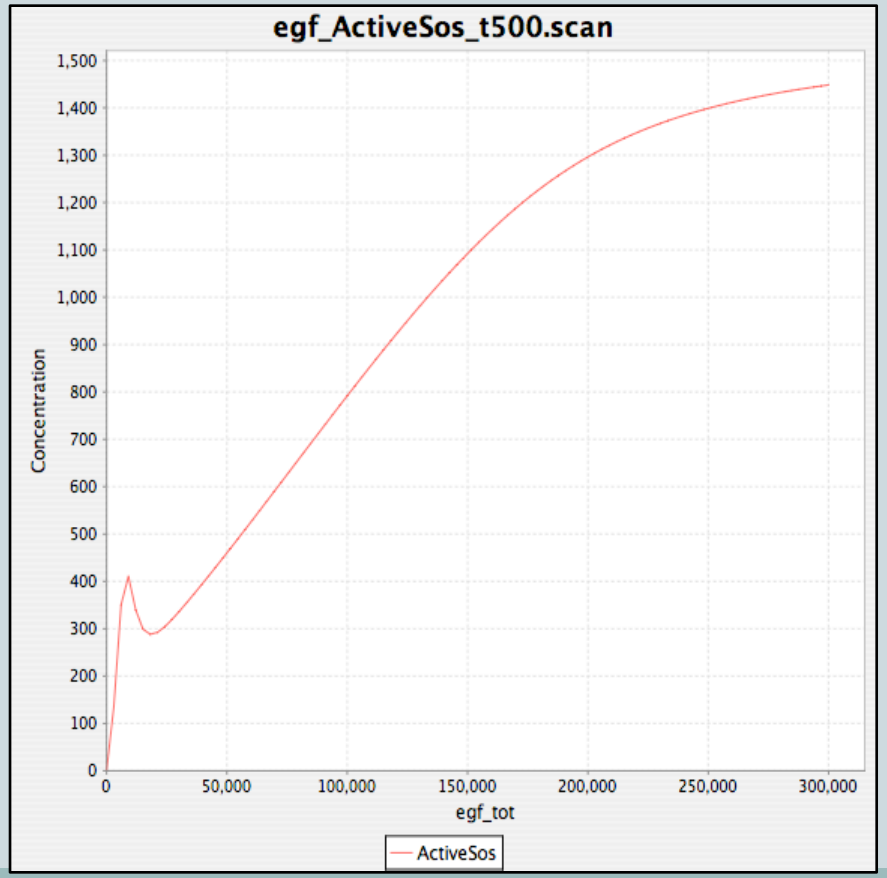


Total Sos activation against egf dose
Time = 200

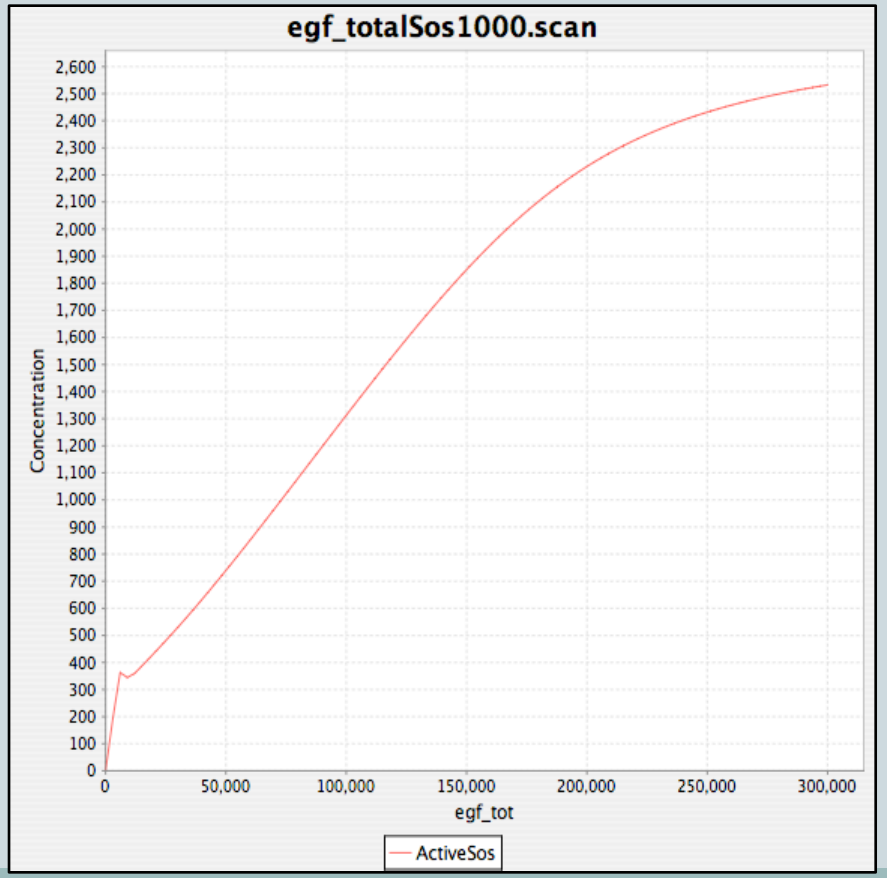


The effect of stimulation on Sos activation: Parameter scan of EGF (ligand) concentration

Total Sos activation against dose
Time = 500

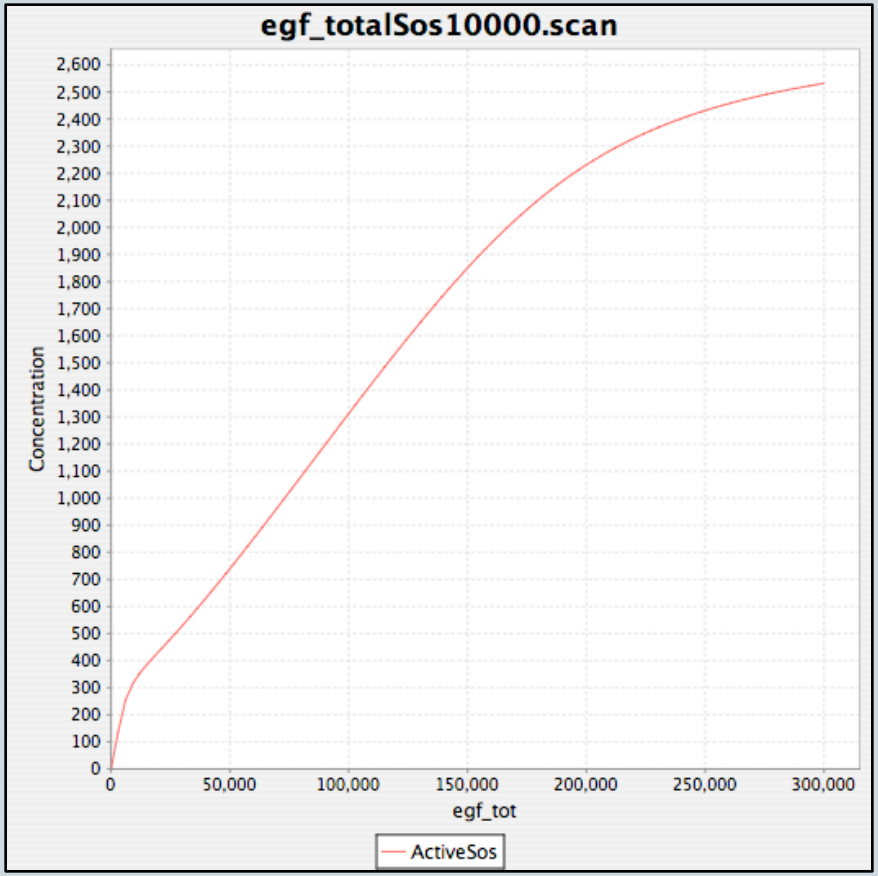


Total Sos activation against egf dose
Time = 1000



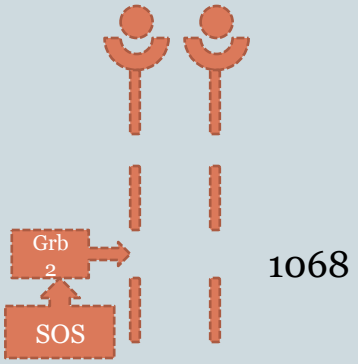
The effect of stimulation on Sos activation: Parameter scan of EGF (ligand) concentration

Total Sos activation against dose
Time = 10000

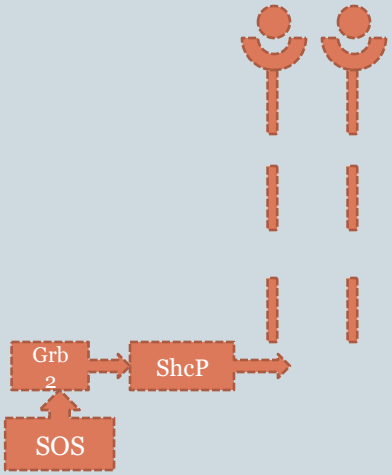


What does it mean?

- Overall, higher amounts of egf correspond to higher Sos activation
- However, the relationship is not monotonic – there is a "valley" where incrementally higher amounts of egf correspond to lower Sos activation
- The valley is less dramatic when the simulation runs for longer time periods
- All results presented are for "EGFR_large" model
- Conjecture: The dual nature of the dose-response curve is due to the two forms of Sos activation (Shc and non-Shc).



1068



1148

Description of Sos activated dimers at different sites and the probabilities of the binding sites.

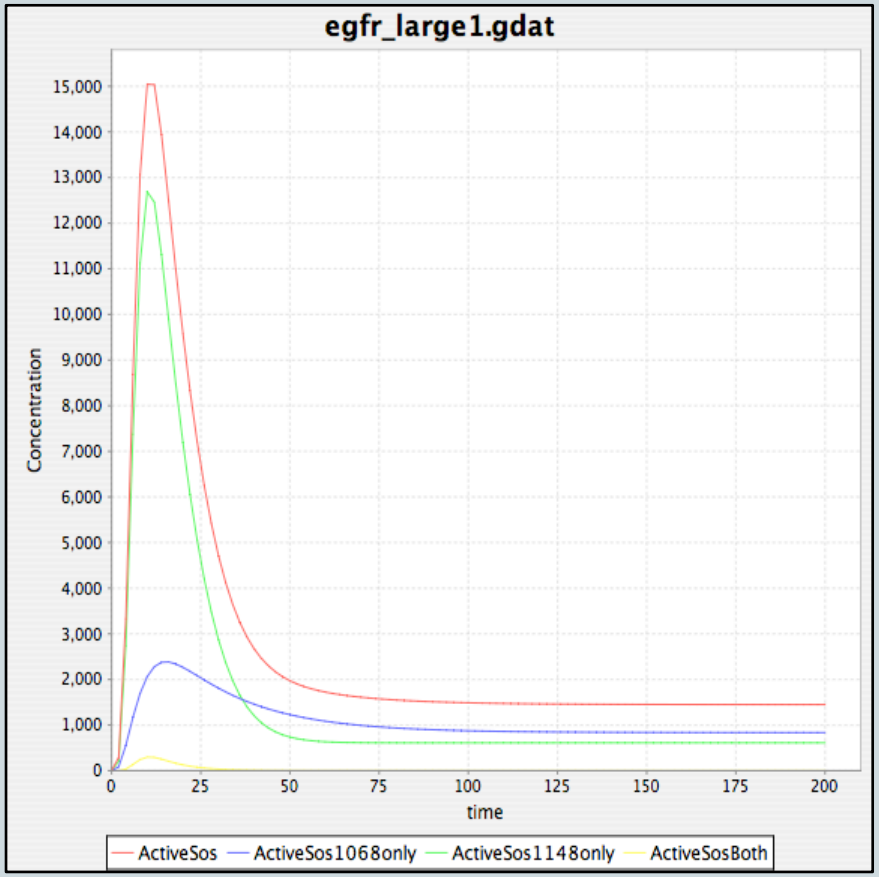
#	1068 (non-Shc) site	1148 (Shc) site	Probabilities
0	0	0	
1	**0**	**1**	**P[Molecule 12]+P[Molecule 14]**
2	0	2	P[(1)]^2
3	**1**	**0**	**P[Molecule 6]+P[Molecule 8]+P[Molecule 9]**
4	**1**	**1**	**P[Molecule 10]**
5	1	1	P[(1)]xP[(3)]
6	1	2	P[(4)]xP[(1)]
7	2	0	P[(3)]^2
8	2	1	P[(4)]xP[(3)]
9	2	2	P[(4)]^2

Codes for the molecules used for the probability table

- 6 Molecules ActiveSos1068a egfr(Y1148,Y1068!1).Grb2(SH2!1,SH3!+)
- 8 Molecules ActiveSos1068b egfr(Y1148!2,Y1068!1).Grb2(SH2!1,SH3!+).Shc(PTB!2,Y317)
- 9 Molecules ActiveSos1068c egfr(Y1148!2,Y1068!1).Grb2(SH2!1,SH3!+).Shc(PTB!2,Y317!3).Grb2(SH2!3,SH3)
- 10 Molecules ActiveSosBoth egfr(Y1148!2,Y1068!1).Grb2(SH2!1,SH3!+).Shc(PTB!2,Y317!3).Grb2(SH2!3,SH3!+)
- 12 Molecules ActiveSos1148a egfr(Y1148!1,Y1068).Shc(PTB!1,Y317!2).Grb2(SH2!2,SH3!+)
- 14 Molecules ActiveSos1148b egfr(Y1148!1,Y1068!3).Shc(PTB!1,Y317!2).Grb2(SH2!2,SH3!+).Grb2(SH2!3,SH3) 15 Molecules ActiveSos1148c

Splitting out the different kinds of Y1068 and Y1148 (Shc site) Sos activation

Total Sos activation

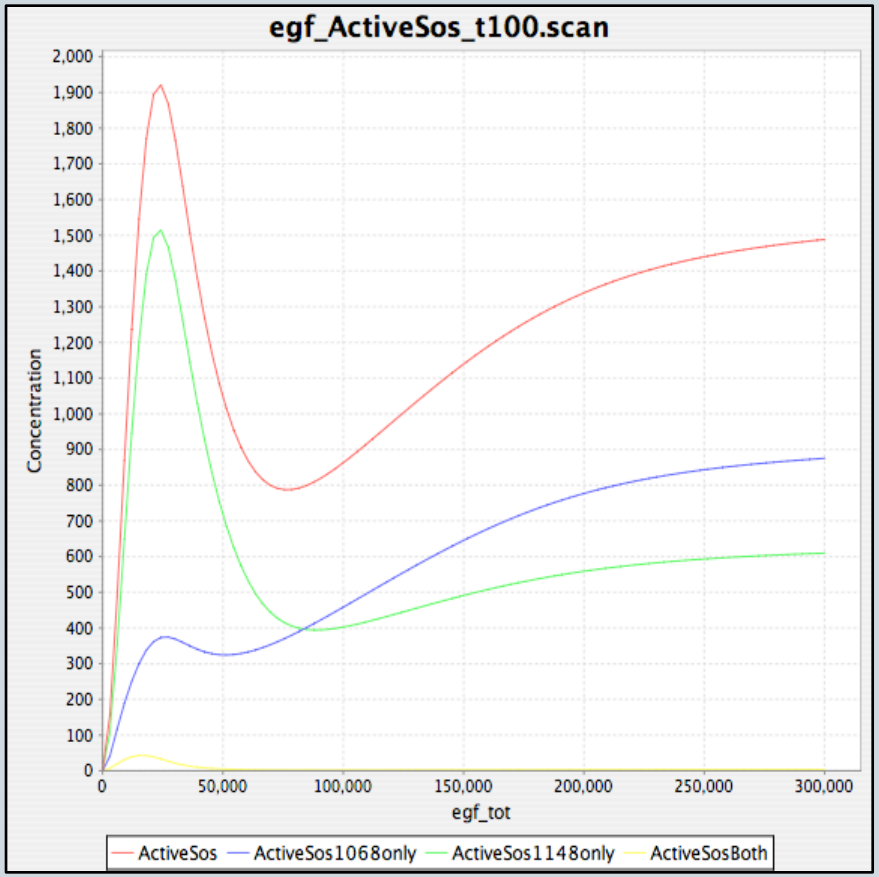


Key

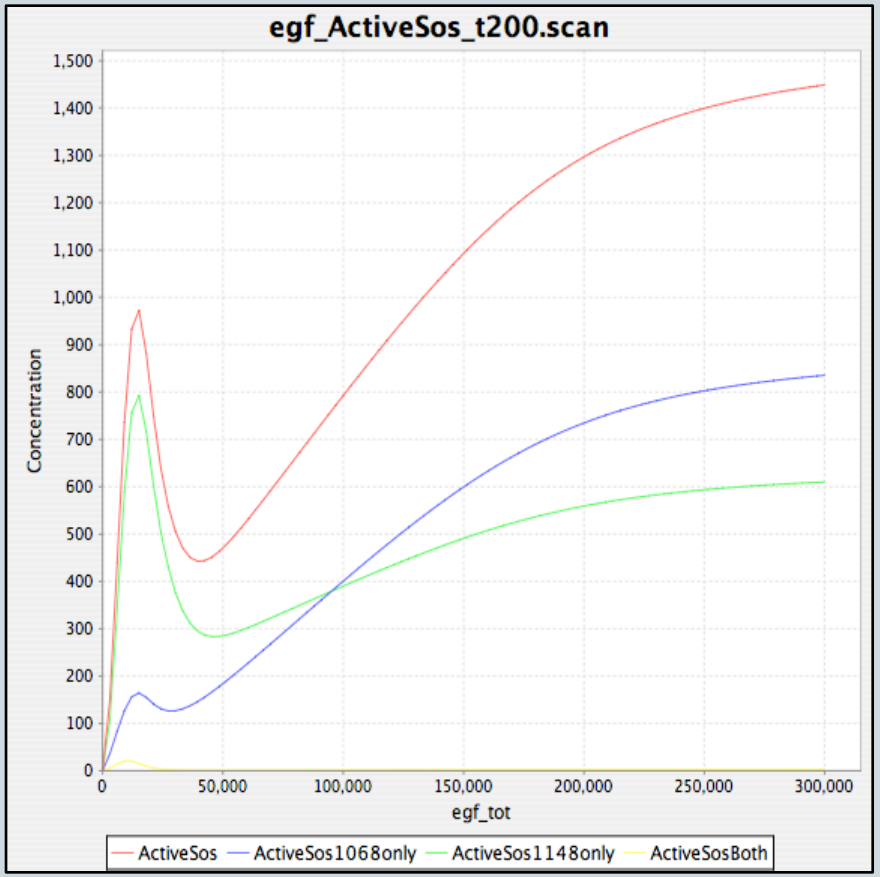
- Red = Total Sos Activation
- Green = Y1148 (Shc site) only activation
- Blue = Y1068 only activation
- Yellow = Sos Activation at both Y1148 and Y1068 sites
- So: **Red** = **Green** + **Blue** – **Yellow**
- Results have been verified through examination of excel data from gdat file

The effect of stimulation on Sos activation: Parameter scan of EGF (ligand) concentration

Total Sos activation against dose
Time = 100

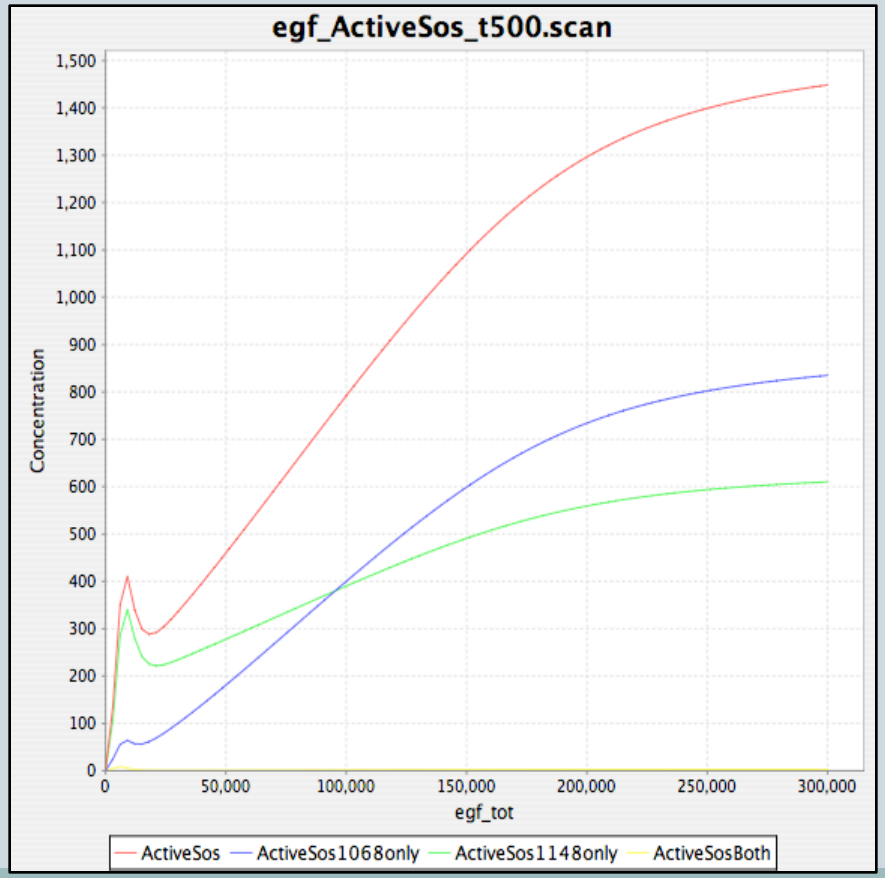


Total Sos activation against egf dose
Time = 200

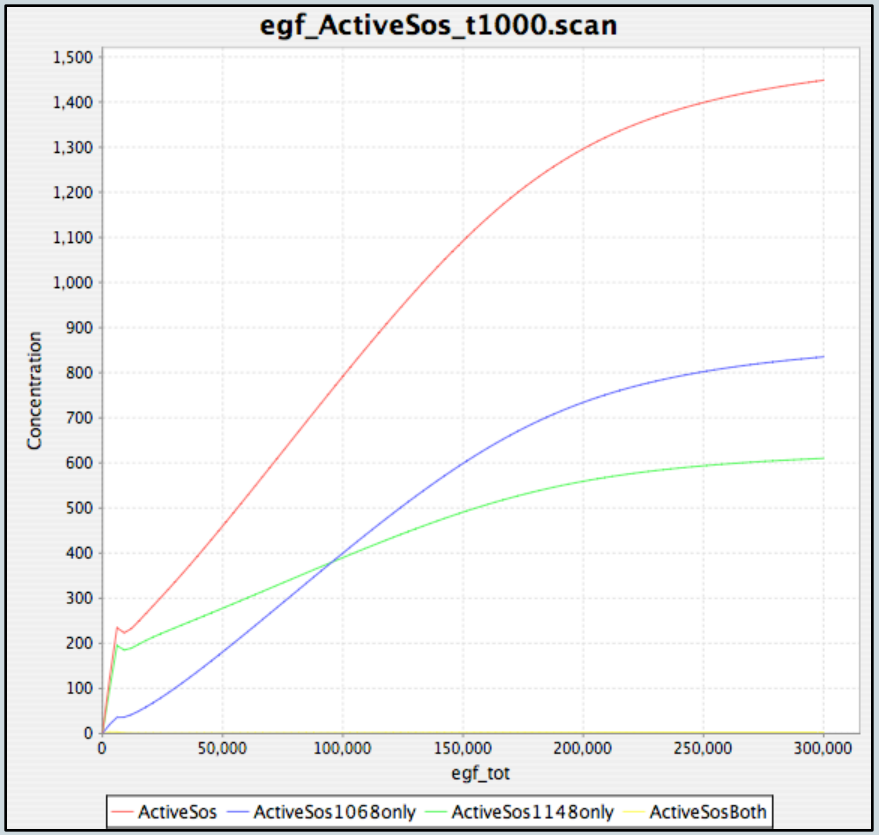


The effect of stimulation on Sos activation: Parameter scan of EGF (ligand) concentration

Total Sos activation against dose
Time = 500

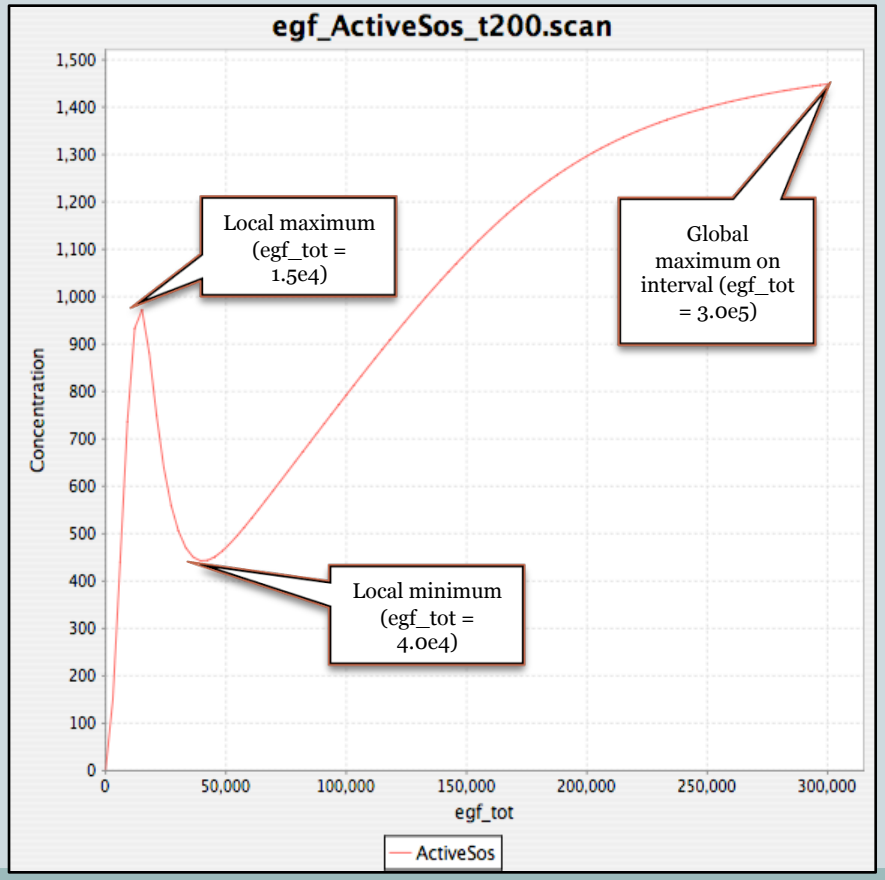


Total Sos activation against egf dose
Time = 1000

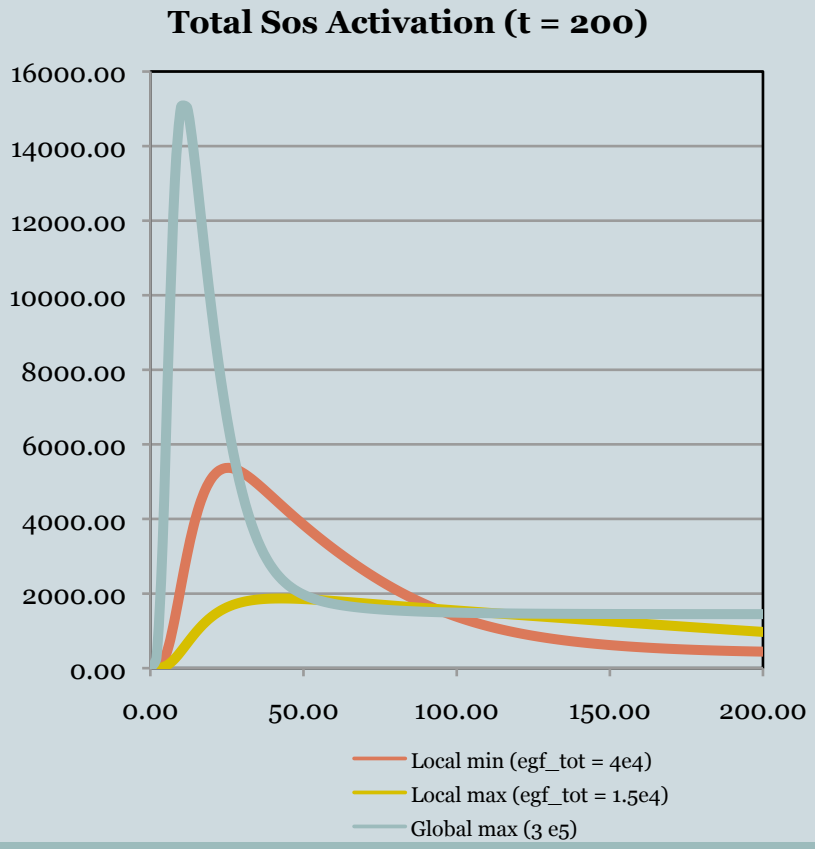


Sos levels reach a peak then decline towards an asymptote over time

Total Sos activation against dose
Time = 200

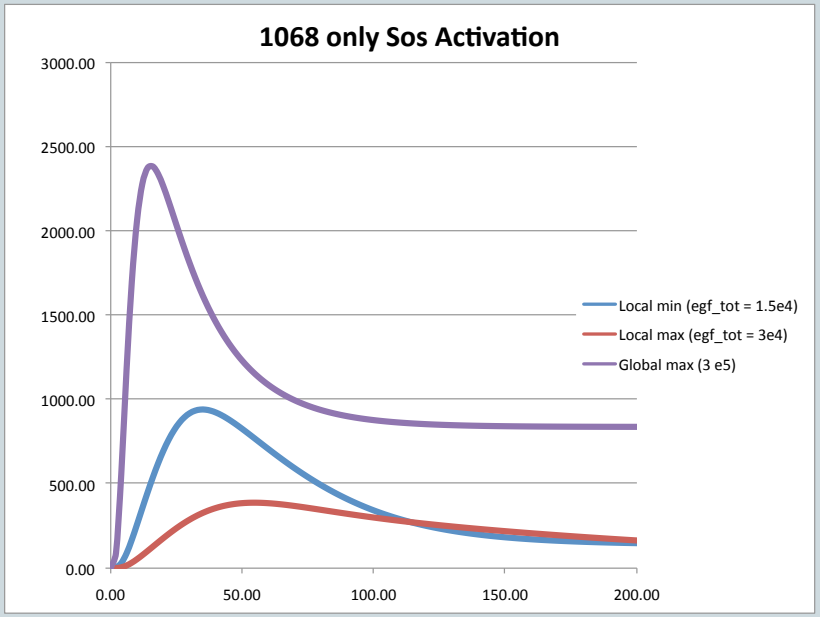


Total Sos activation against time for three initial values of ligand concentration (egf_tot)

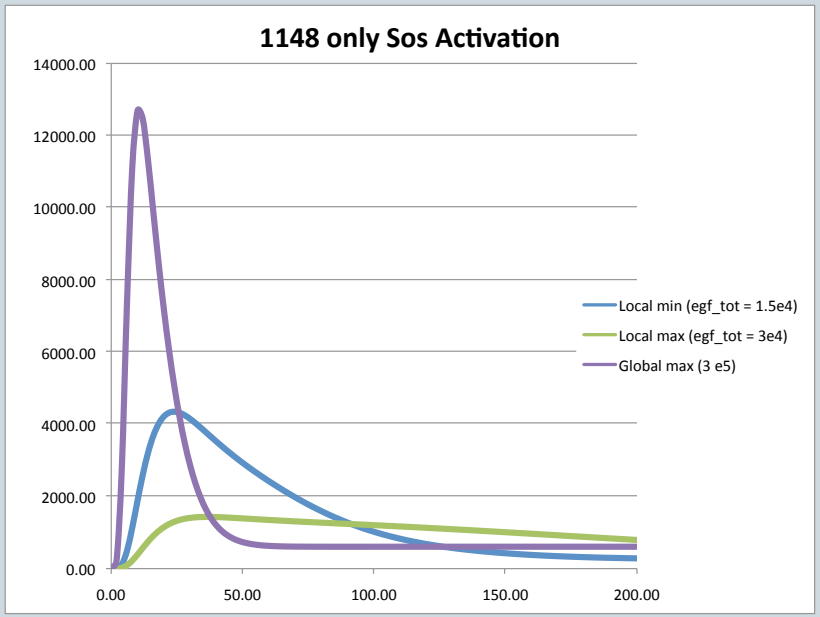


Sos Activation by phosphorylation site

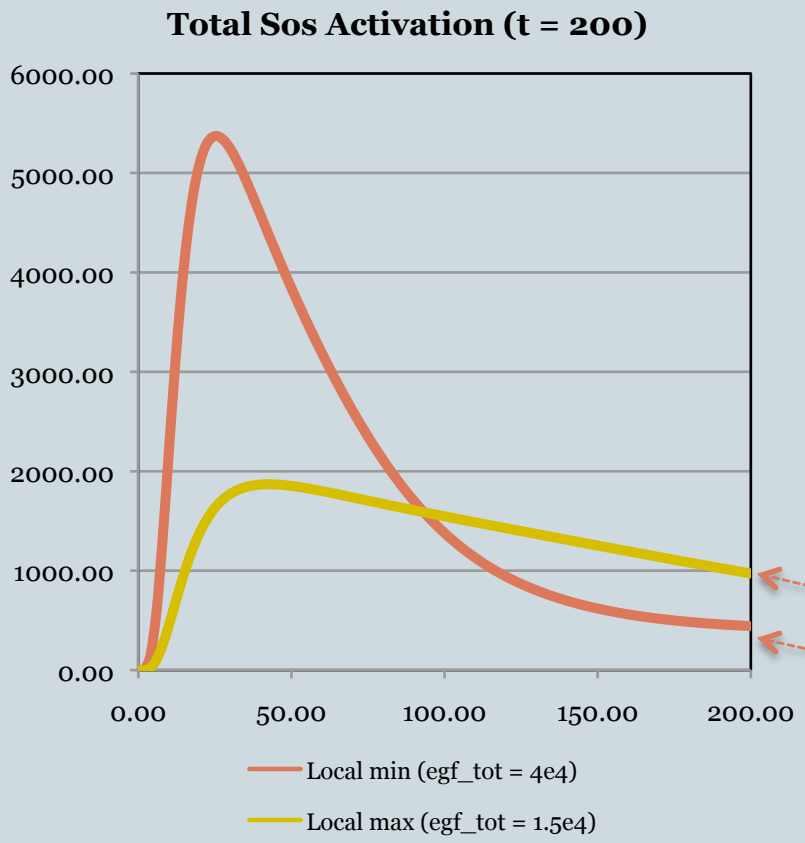
1068 Sos activation against time for three initial values of ligand concentration (egf_tot)



1148 Sos activation against time for three initial values of ligand concentration (egf_tot)

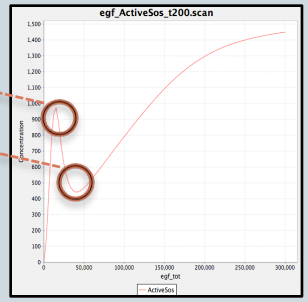


Sos levels reach a peak then decline towards an asymptote over time

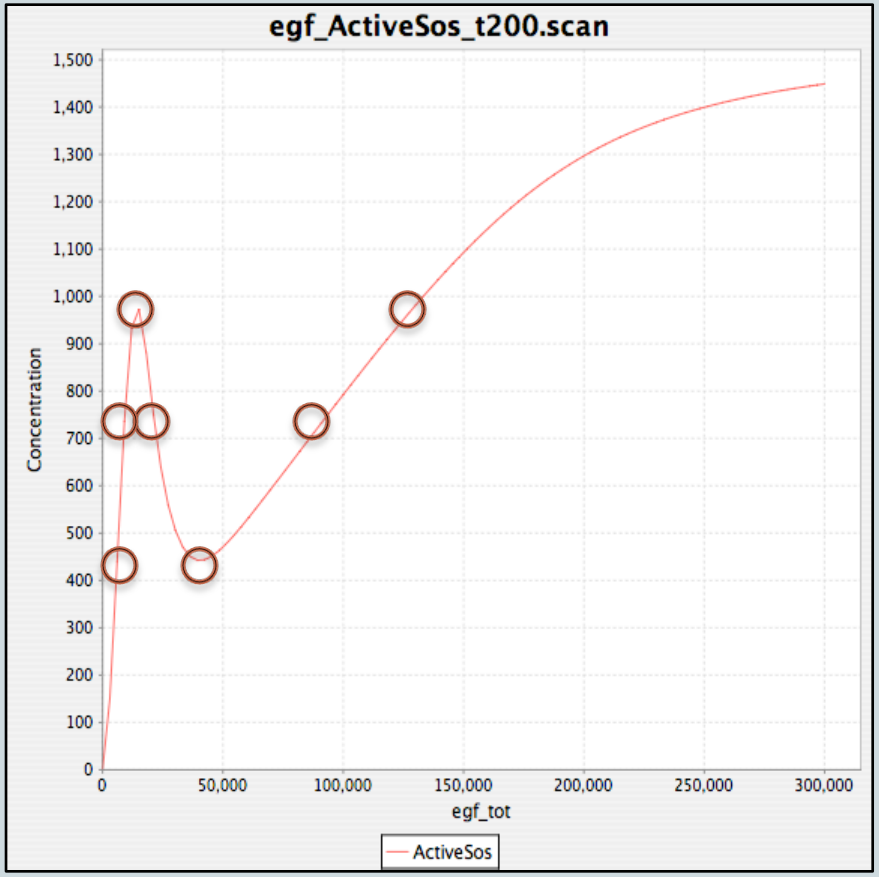


Total Sos activation against time for three initial values of ligand concentration (egf_tot)

- The dose response curves represent the value of Active Sos at the end of the run (i.e. the low values on the right hand side of this graph)
- The graphs for larger values of time suggest that the asymptotic final value of active Sos is proportional to the initial ligand concentration (e.g. the approximately linear dose response curve for t = 10,000)
- The local maximum present in the dose response curves for lower values of time (e.g. t = 200) may indicate qualitatively different Sos Activation behavior



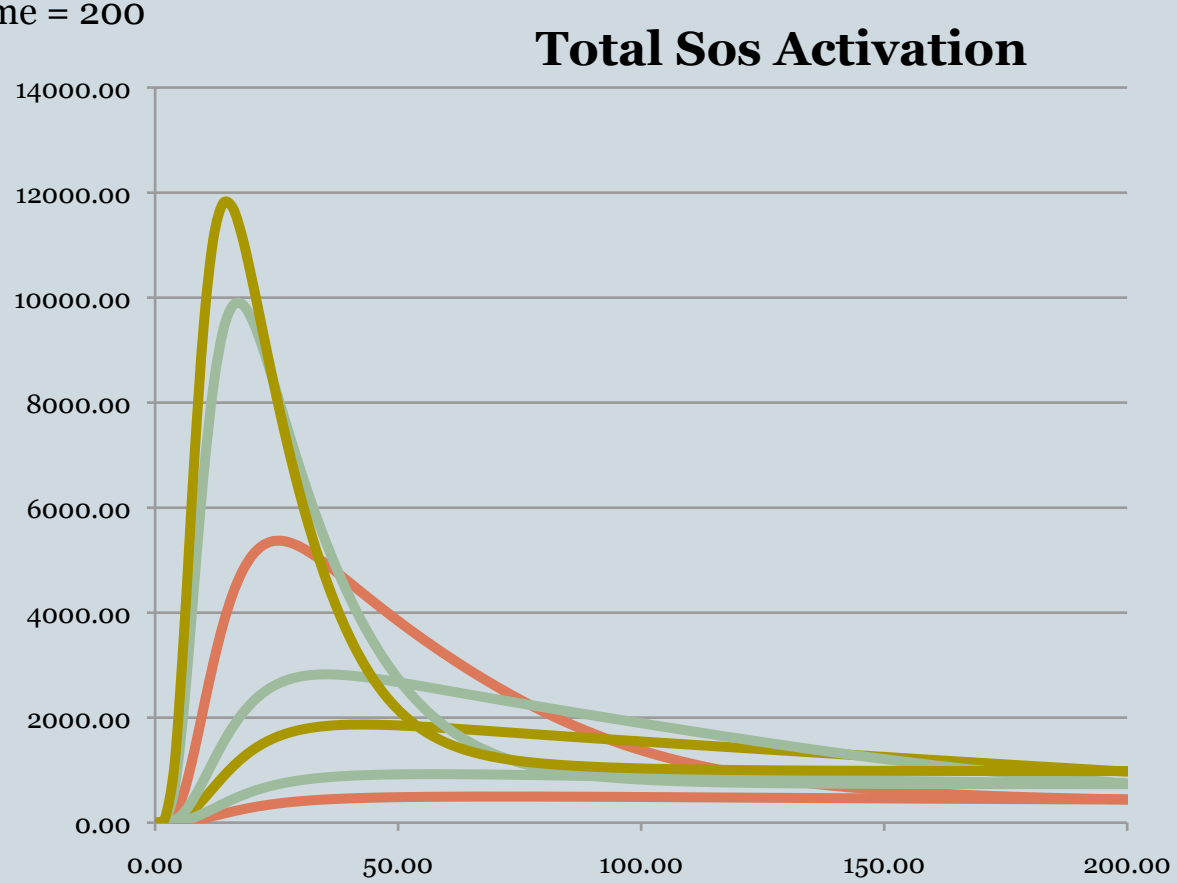
Sos activation behavior differed according to initial egf concentration, but relation was not one-to-one

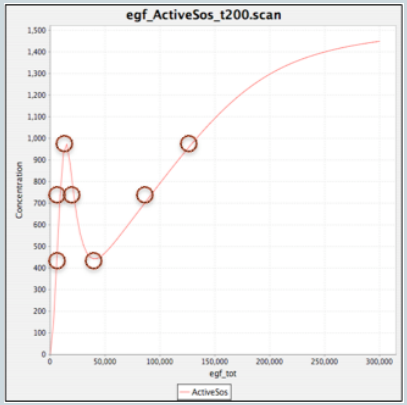


Sos Activation by phosphorylation site

Total Sos activation for various dose levels

Time = 200

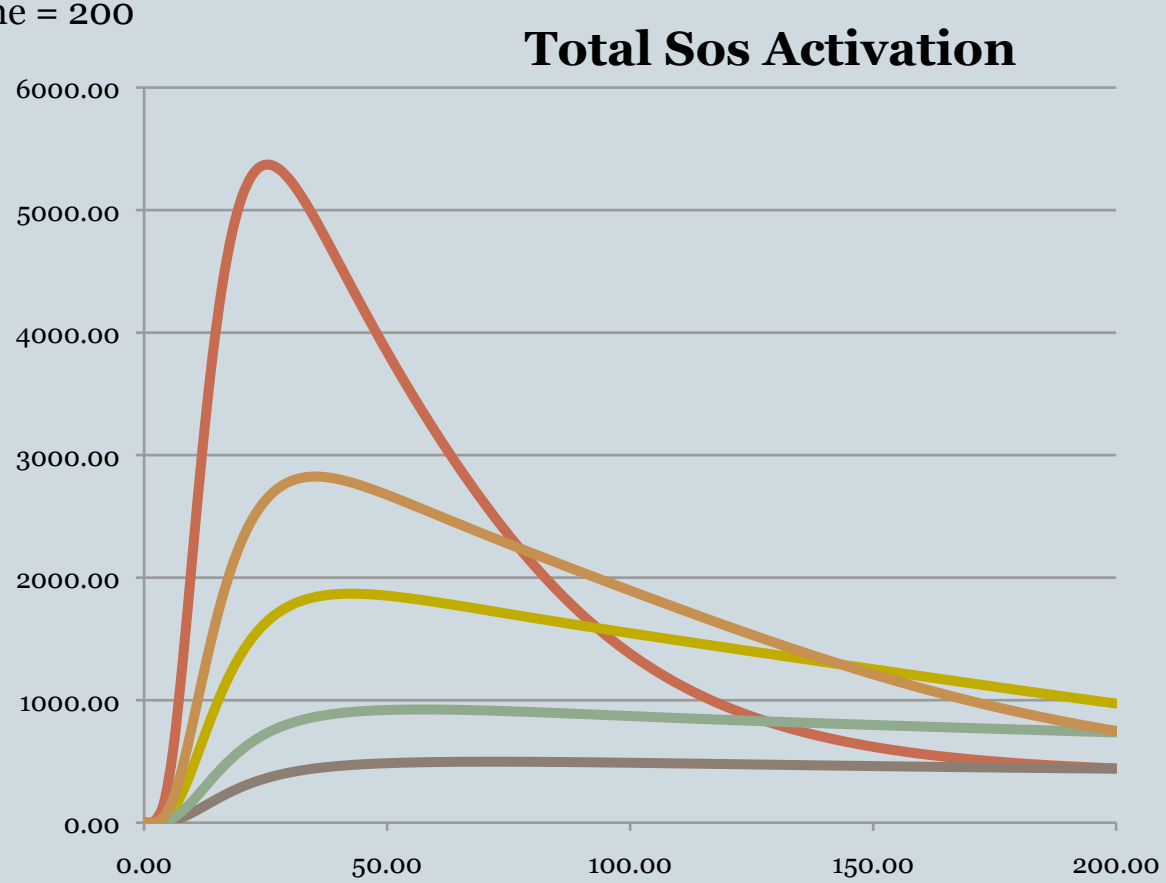


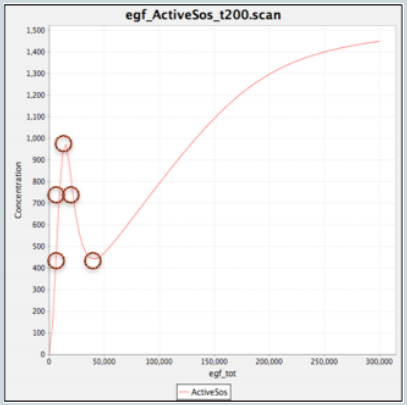


Sos Activation by phosphorylation site

Total Sos activation for various dose levels

Time = 200





Some summary thoughts

- Peak-and-valley behavior probably not due to differences in 1068 and 1148 Sos activation
- May be due to a threshold criterion for Sos in the first 50 seconds
- Levels of Active Sos are proportional to initial egf concentration as time approaches infinity (reflected in linear pattern of t=10,000 dose-response curve)