

RAS FEEDBACK

Ras increases SOS activity

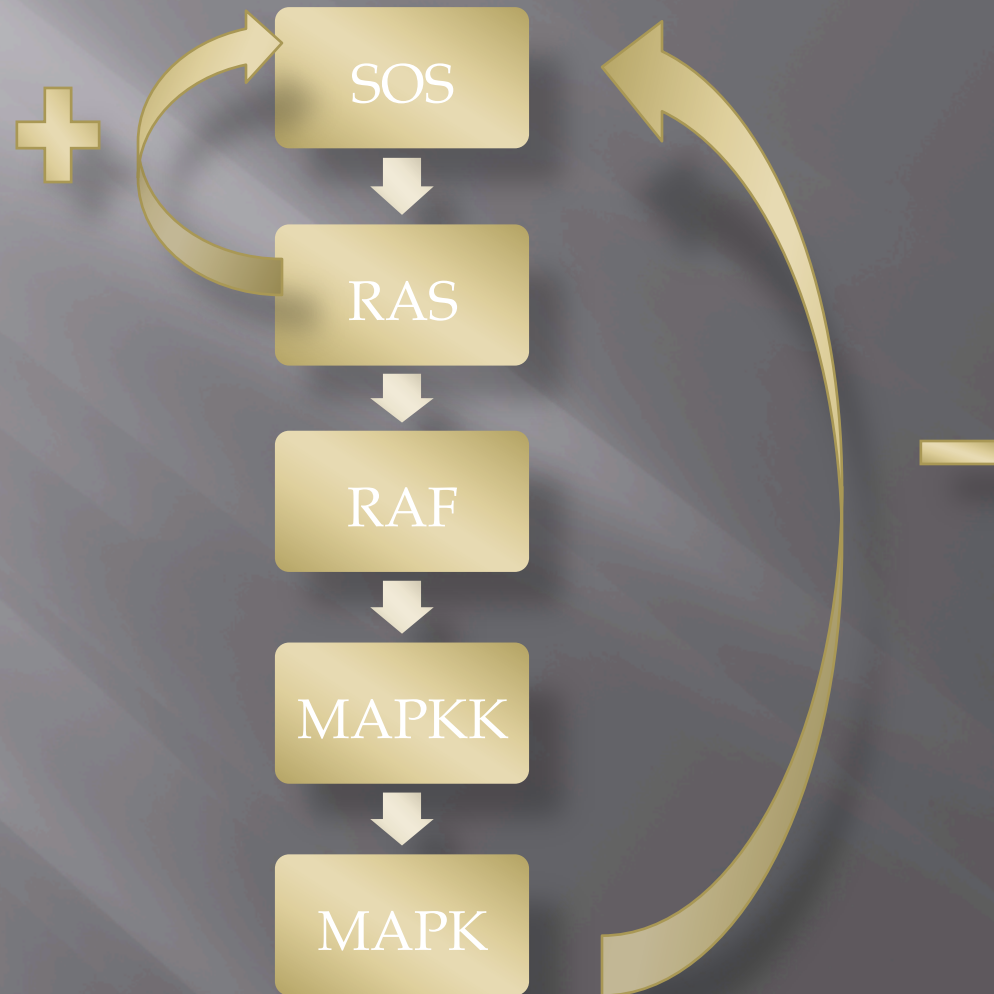
Introduction



EGFR recruits SOS to the plasma membrane which facilitates the switch from Ras-GDP (off) to Ras-GTP (on)

SOS-Ras complex catalyzes a positive feedback reaction.

Introduction



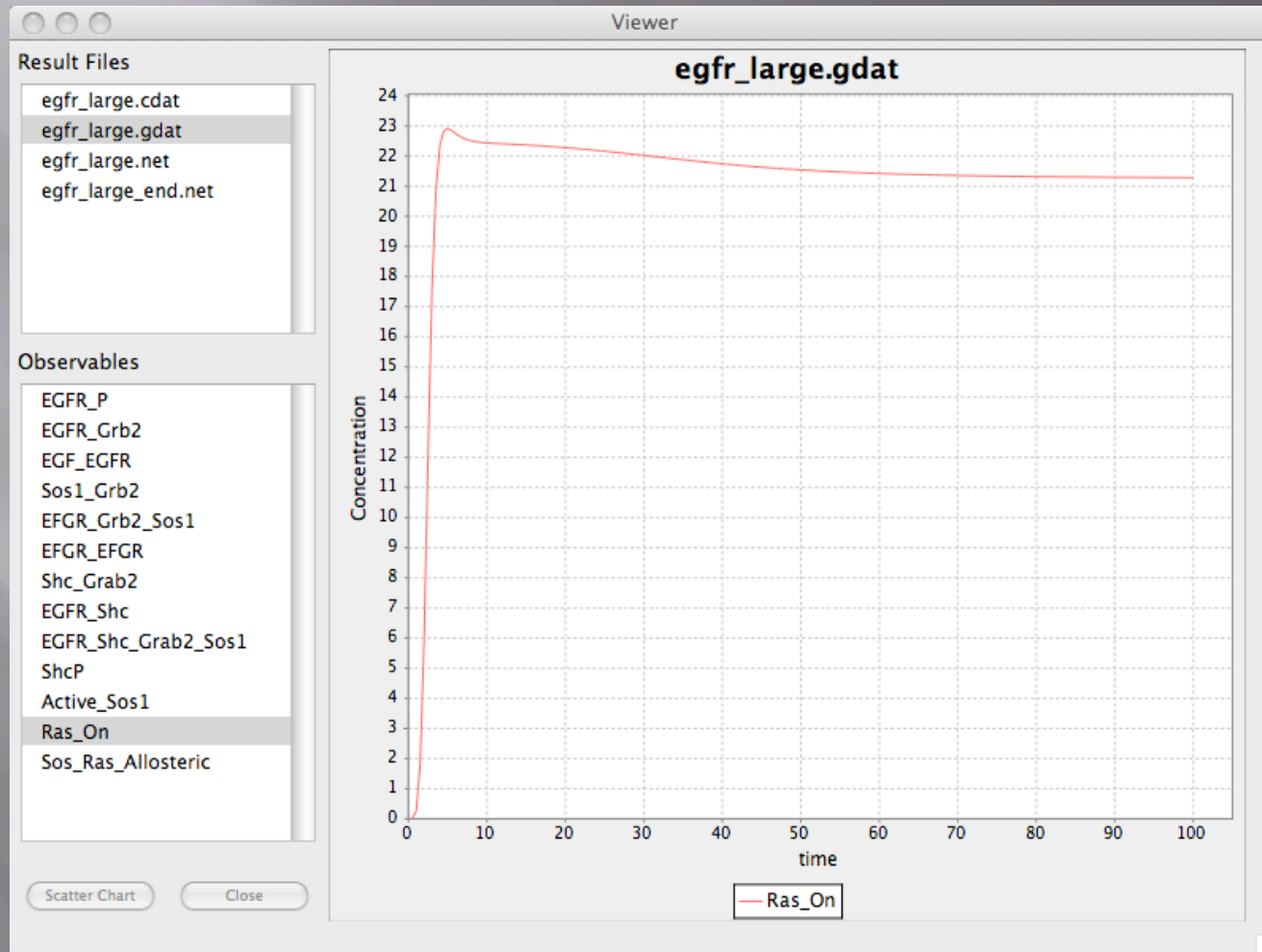
Hypothesis

The effect of a positive feedback of Ras is an increased SOS activity, which causes Ras to be activated at a greater rate.

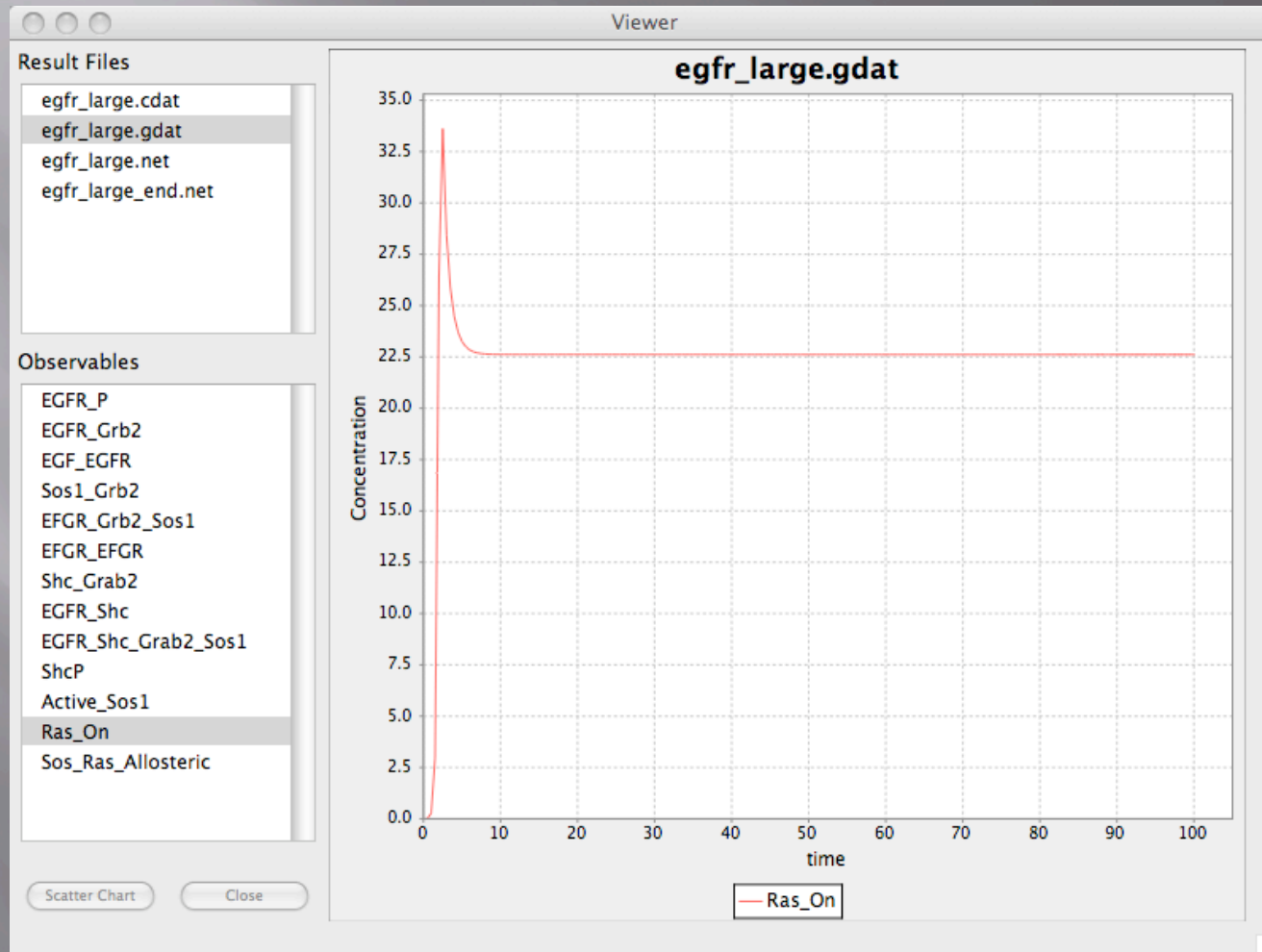
Analysis: Model

```
Untitled
Styles Spacing Lists
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
begin parameters
.
.
.
Ras_tot 50
kp26 0.5 # Ras Activation
km26 0.01 # Ras Deactivation
kp28 0.03 # Ras binding to allosteric Sos
km28 0.064 # Ras dissociating from allosteric Sos
kp26a 37.5 # Ras Activation allosteric
km26a 0.01 # Ras Deactivation allosteric
.
.
end parameters
begin reaction rules
.
.
.
# Ras
egfr(Y1148~pY12).Shc(PTB!2,Y317~pY11).Grb2(SH2!1,SH3!3).Sos(dom!3,all) + Ras(s~off) -> Ras(s~on) + egfr(Y1148~pY12).Shc(PTB!2,Y317~pY11).Grb2(SH2!1,SH3!3).Sos(dom!3,all) kp26
egfr(Y1068~pY11).Grb2(SH2!1,SH3!2).Sos(dom!2,all) + Ras(s~off) -> Ras(s~on) + egfr(Y1068~pY11).Grb2(SH2!1,SH3!2).Sos(dom!2,all) kp26
Ras(s~on) -> Ras(s~off) km26
Ras(s~on) + Sos(all) <-> Ras(s~on!1).Sos(all!1) kp28,km28
Ras(s~?!1).Sos(all!1) -> Ras(s~?) + Sos(all) kp26
# Ras effect
egfr(Y1148~pY12).Shc(PTB!2,Y317~pY11).Grb2(SH2!1,SH3!3).Sos(dom!3,all!) + Ras(s~off) -> Ras(s~on) + egfr(Y1148~pY12).Shc(PTB!2,Y317~pY11).Grb2(SH2!1,SH3!3).Sos(dom!3,all!) kp26a
egfr(Y1068~pY11).Grb2(SH2!1,SH3!2).Sos(dom!2,all!) + Ras(s~off) -> Ras(s~on) + egfr(Y1068~pY11).Grb2(SH2!1,SH3!2).Sos(dom!2,all!) kp26a
.
.
end reaction rules
```

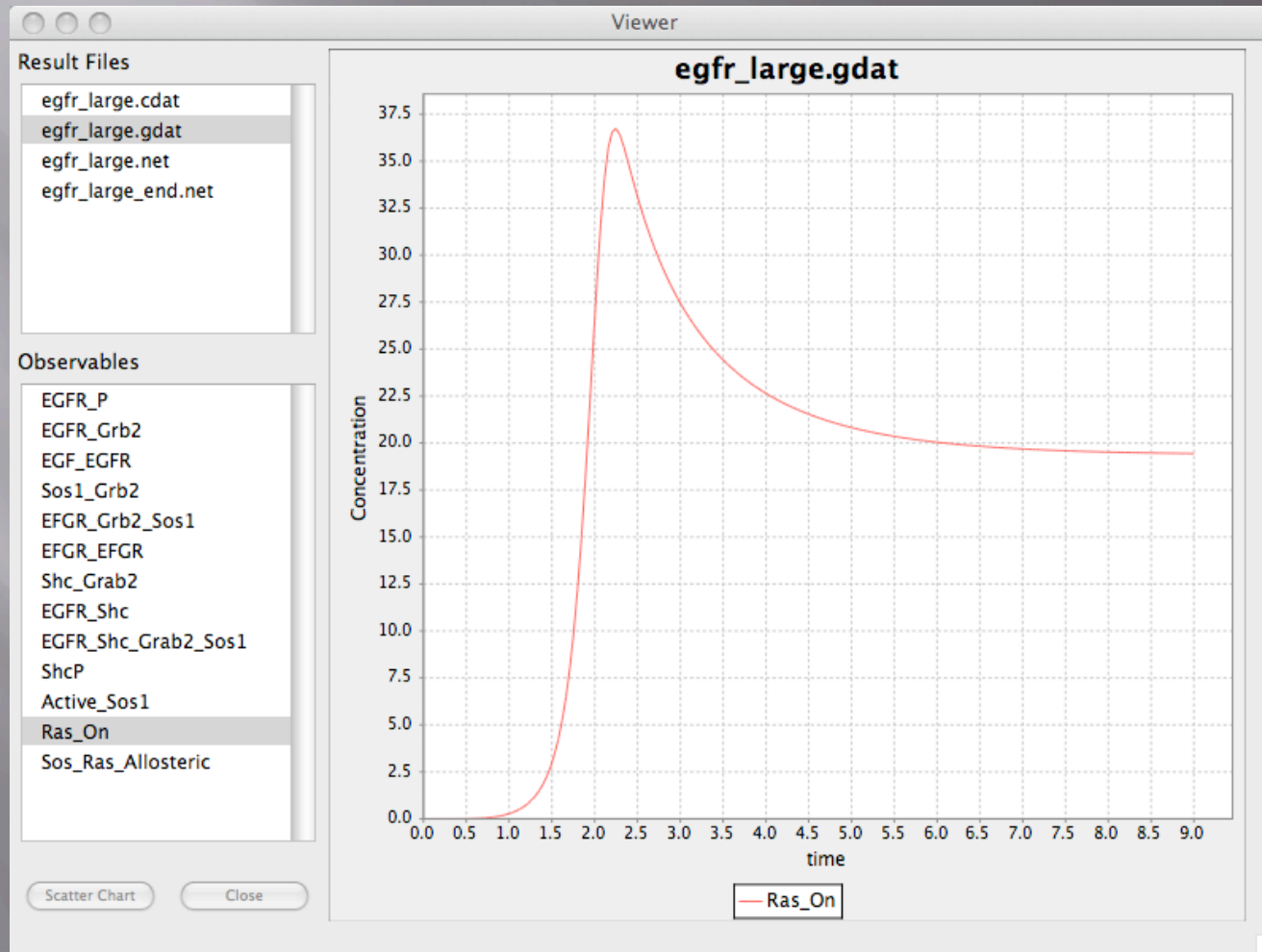
Analysis: Graphs



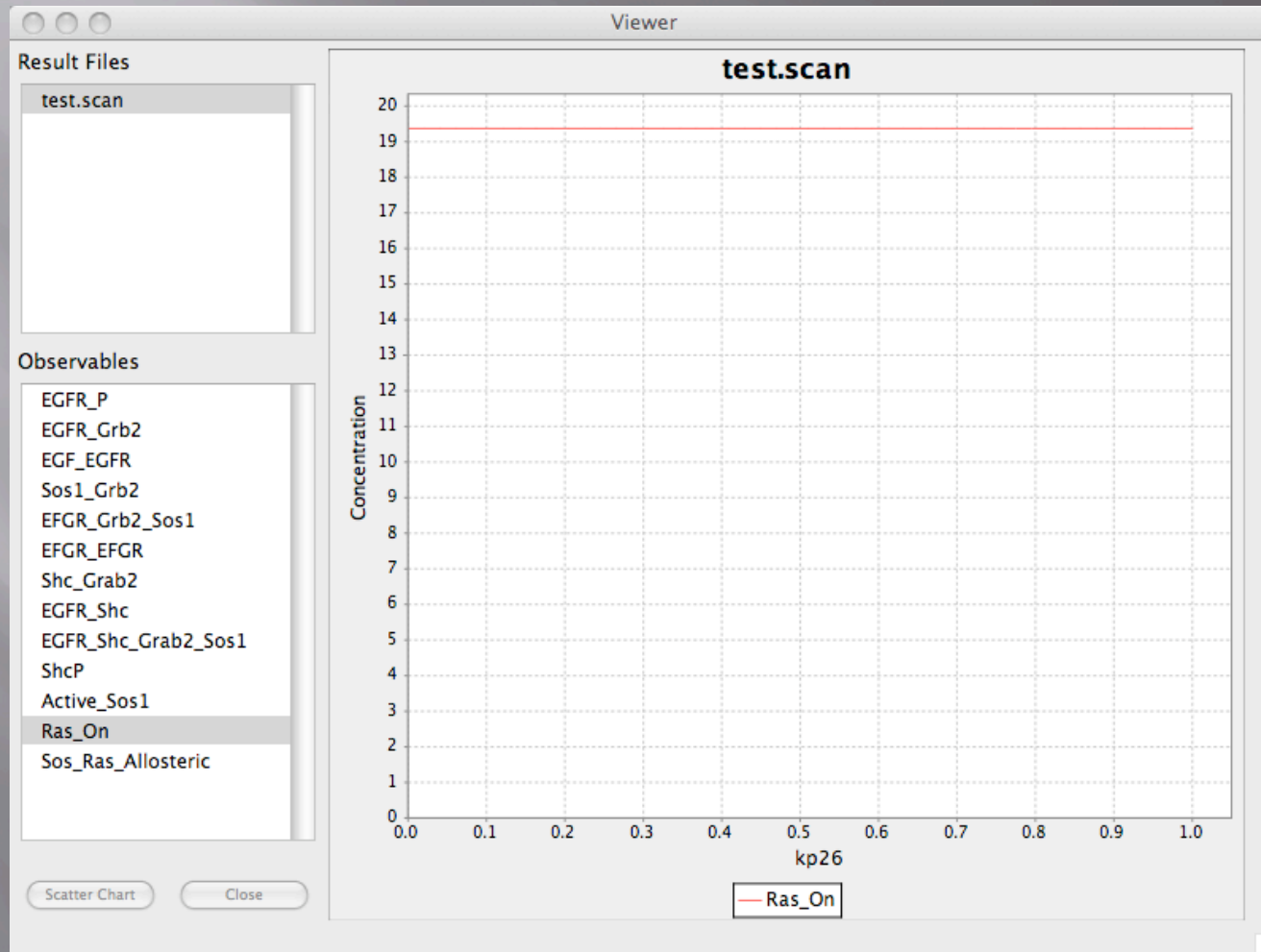
Analysis: Graphs



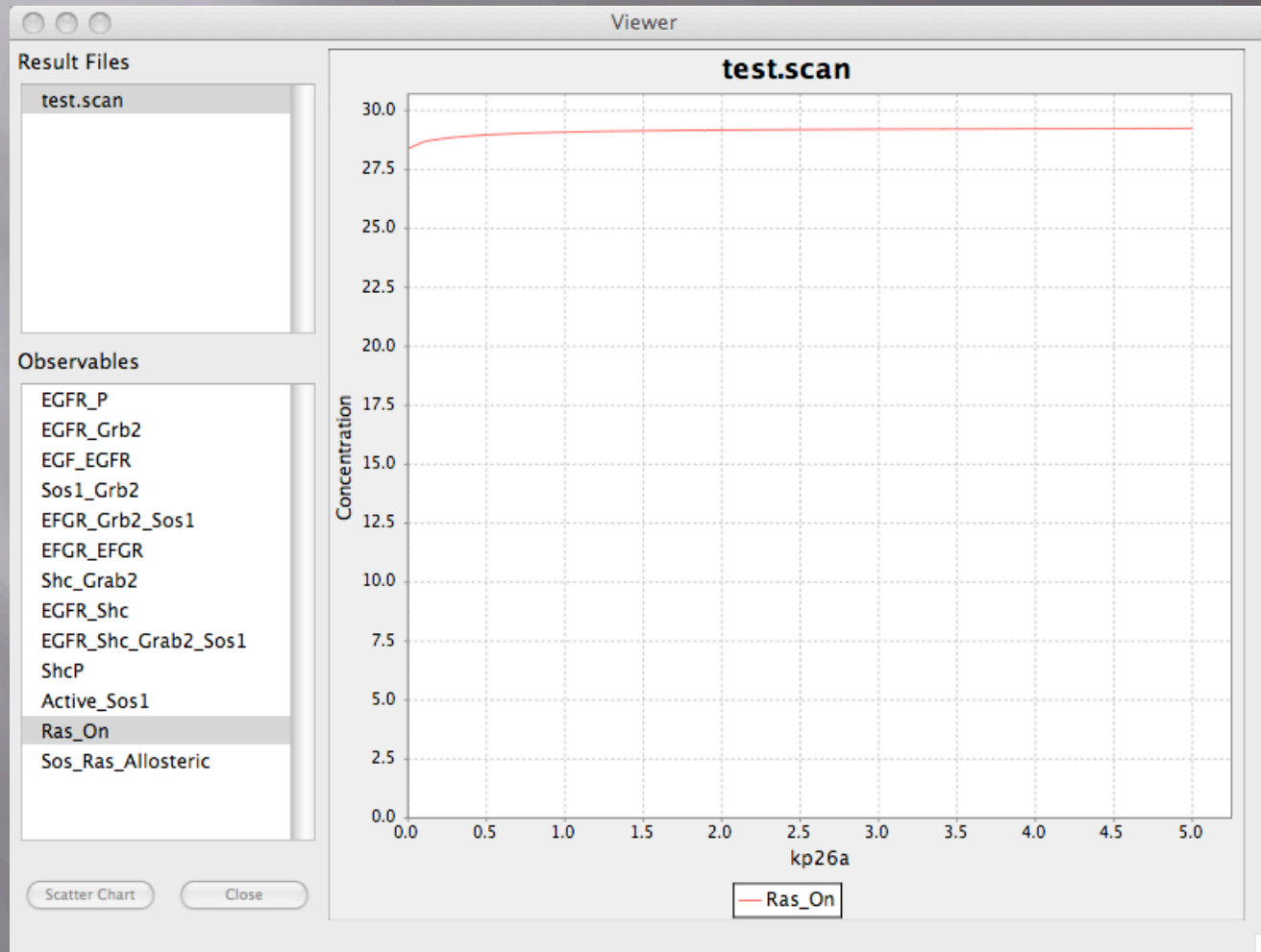
Analysis: Graphs



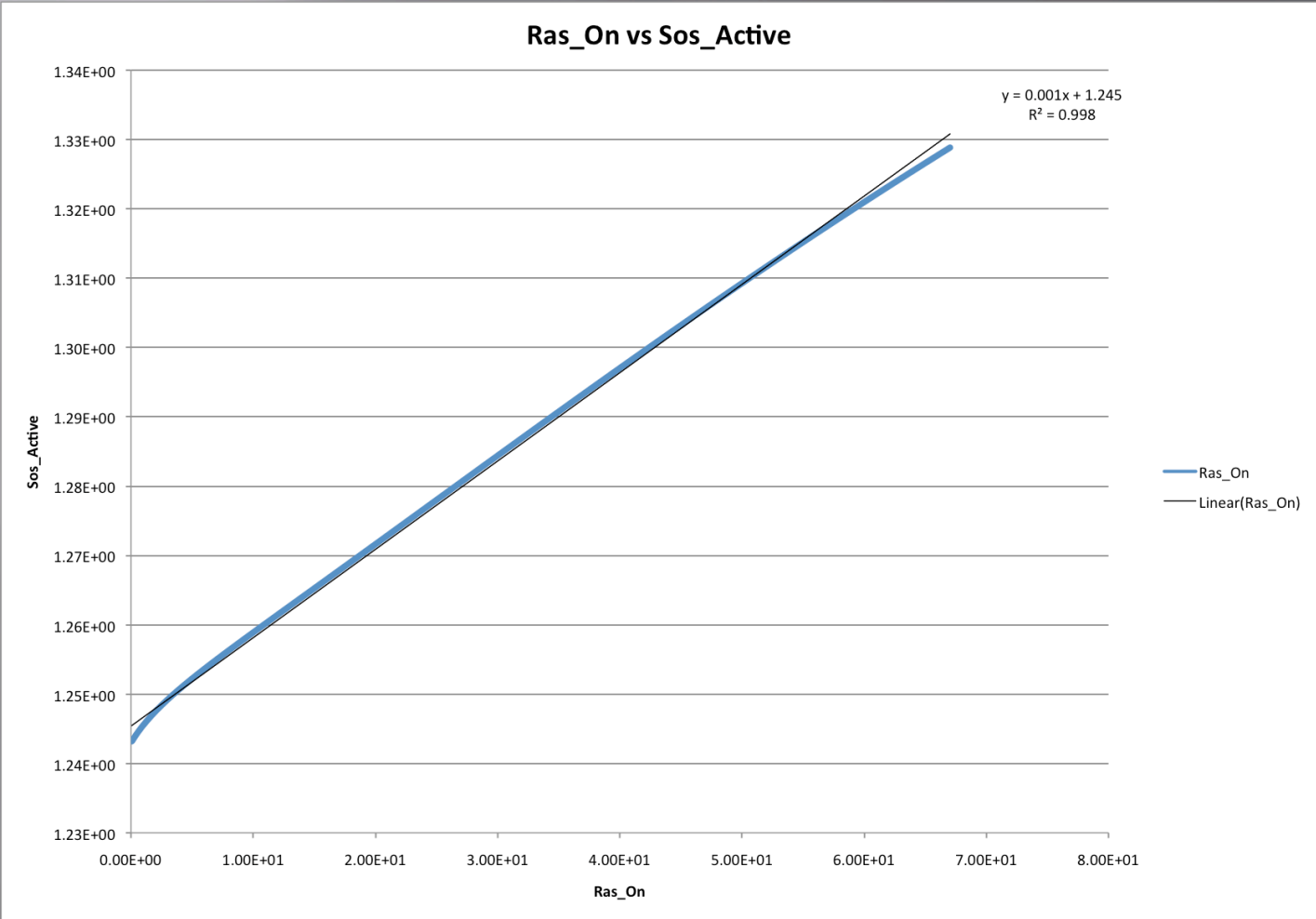
Analysis: Graphs



Analysis: Graphs



Analysis: Graphs



Discussion

- ▣ Assumptions: Rate Constants
 - Ras activation by SOS
 - ▣ Mechanism similar to transphosphorylation
 - 0.5 for dimer and for PLCg, so used 0.5 for Ras also
 - Ras binding/dissociation to/from SOS' allosteric site
 - ▣ Binding rates are less than dissociation rates
 - Used Sch-Grb2 binding rates to SOS (0.03/0.064)
 - Ras activation by SOS-Ras complex
 - ▣ Activation rate is increased 75 fold (according to Jim)
 - Multiplied assumption for SOS activation by 75 (37.5)
 - Ras deactivation
 - ▣ Similar to dephosphorylation
 - Used dephosphorylation rate for PLCg in cytosol (0.01)

Conclusions

- ❑ Ras attaches to Sos at an allosteric site. This complex acts as an enzyme which catalyzes the rate of Sos binding.
- ❑ The increase in the Ras concentration results in a positive feedback loop on Sos mediated activation.
- ❑ Ras has no effect on the other observables.
- ❑ Ras self-regulates by switching off, thereby concluding the feedback reaction.

References

- ▣ Finding the right model
 - Asked Jim
 - Research
 - ▣ Useful articles
 - Structural Evidence for Feedback Activation by the Ras-GTP of the Ras-Specific Nucleotide Exchange Factor SOS
 - Margarit et al., 2003
 - Digital Signaling and Hysteresis Characterize Ras Activation in Lymphoid Cells
 - Das et al., 2008
 - ▣ Wikipedia

Comments and Questions

