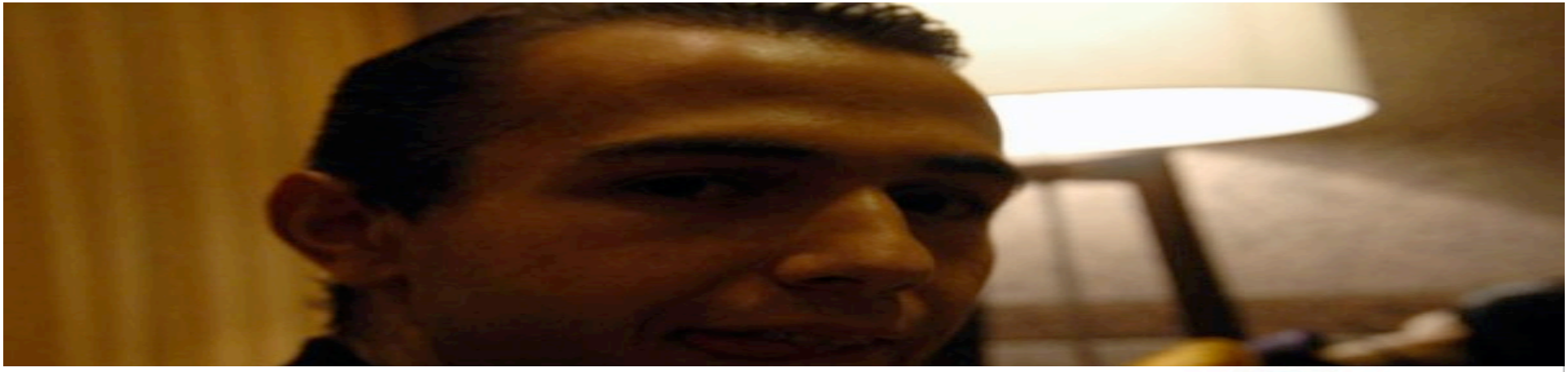
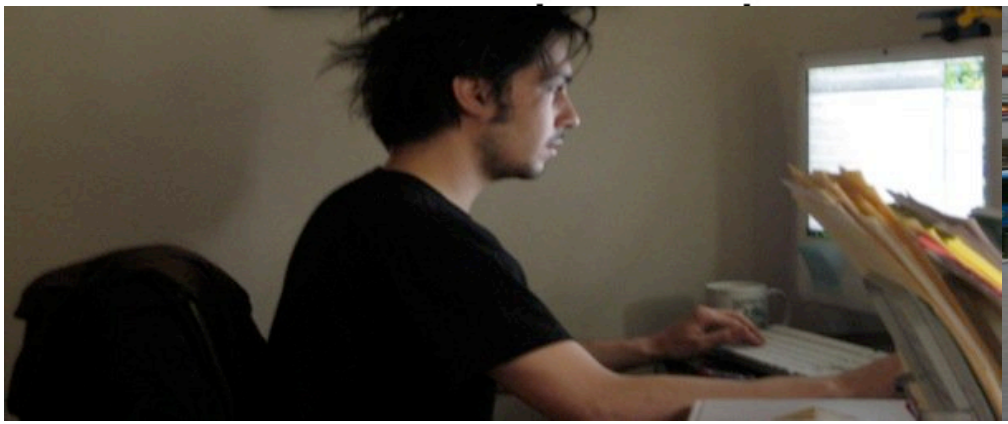


CMACS

Computational **M**odeling and **A**nalysis for **C**omplex **S**ystems



LEHMAN COLLEGE
WINTER 2010

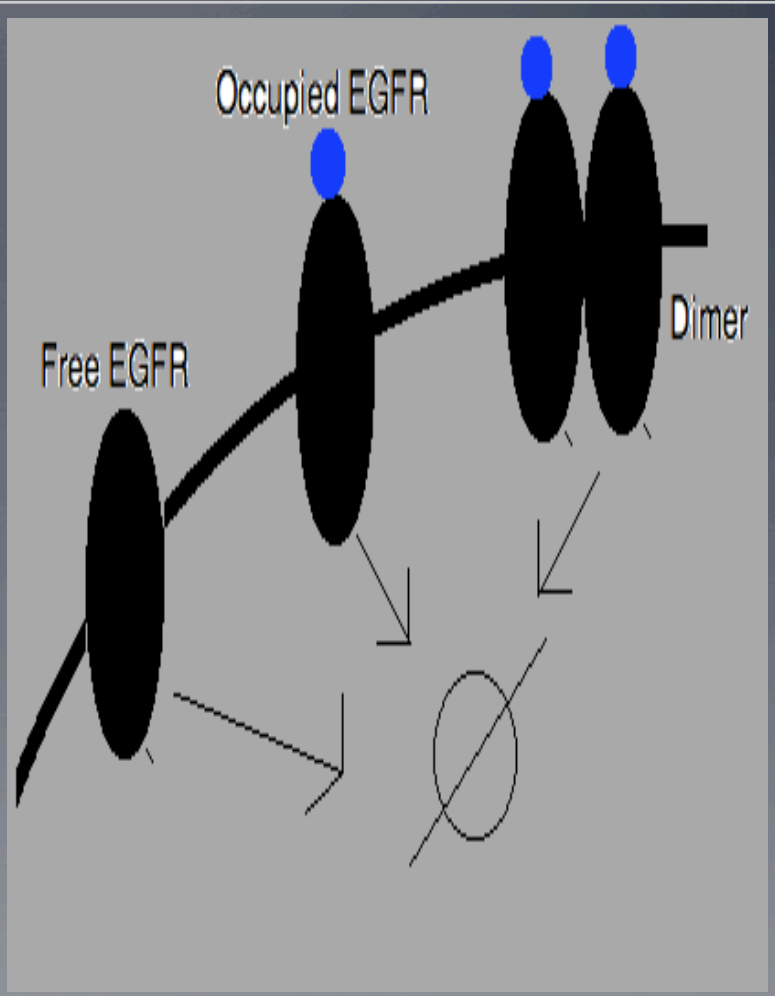
Modeling Degradation of EGFR

- How long does EGFR stay bound to the membrane?
- What factors affect EGFR longevity?

Experimental Simplifications

1) Degradation and Internalization are the same process

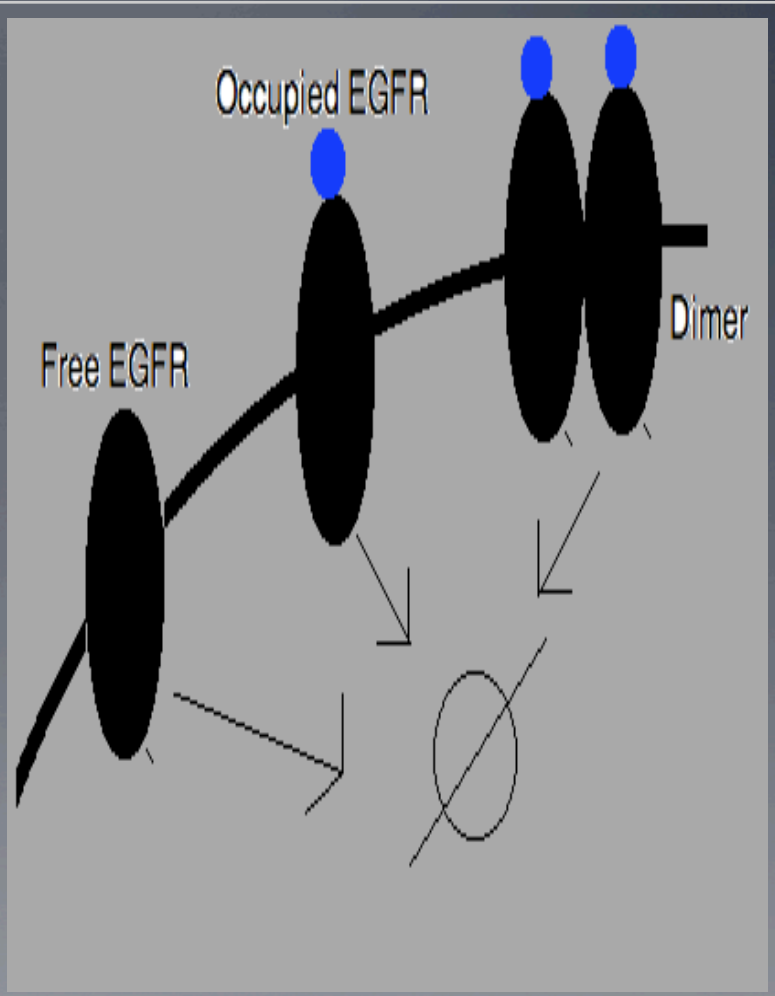
   Most EGFR leaves membrane by way of internalization



Experimental Simplifications

2) Rate of degradation is independent of EGFR state

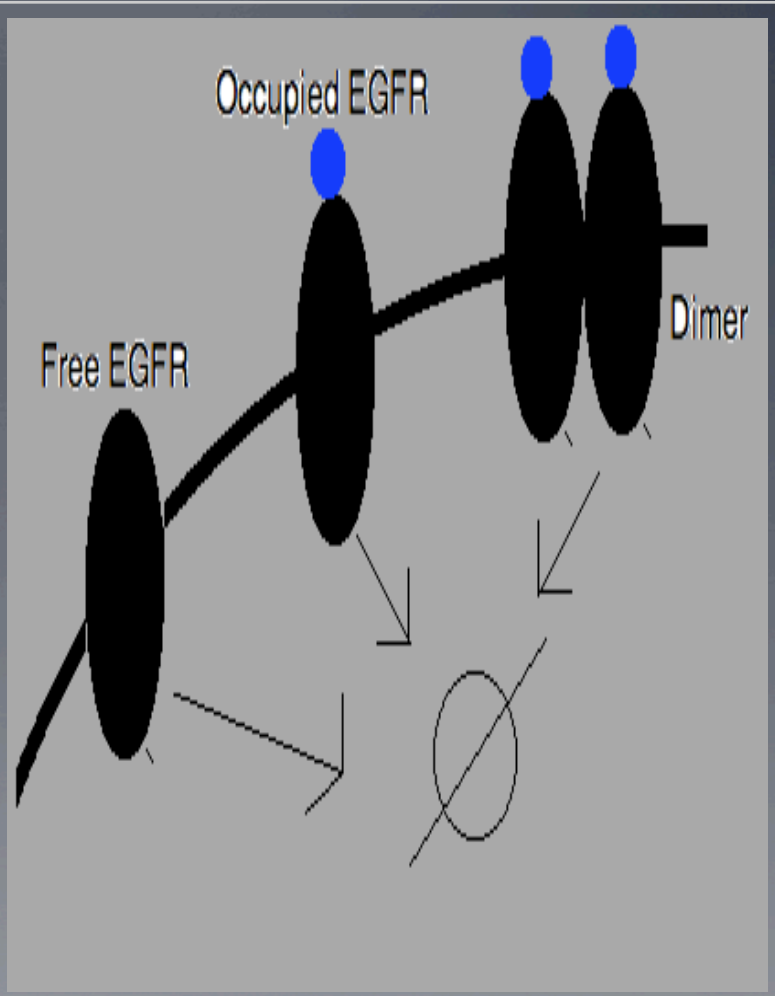
   Occupied and phosphorylated EGFR are internalized at a higher rate



Experimental Simplifications

3) EGFR is never recycled back into the membrane

   EGFR is recycled back into the membrane in at least two distinct mechanisms



BNG Implementation

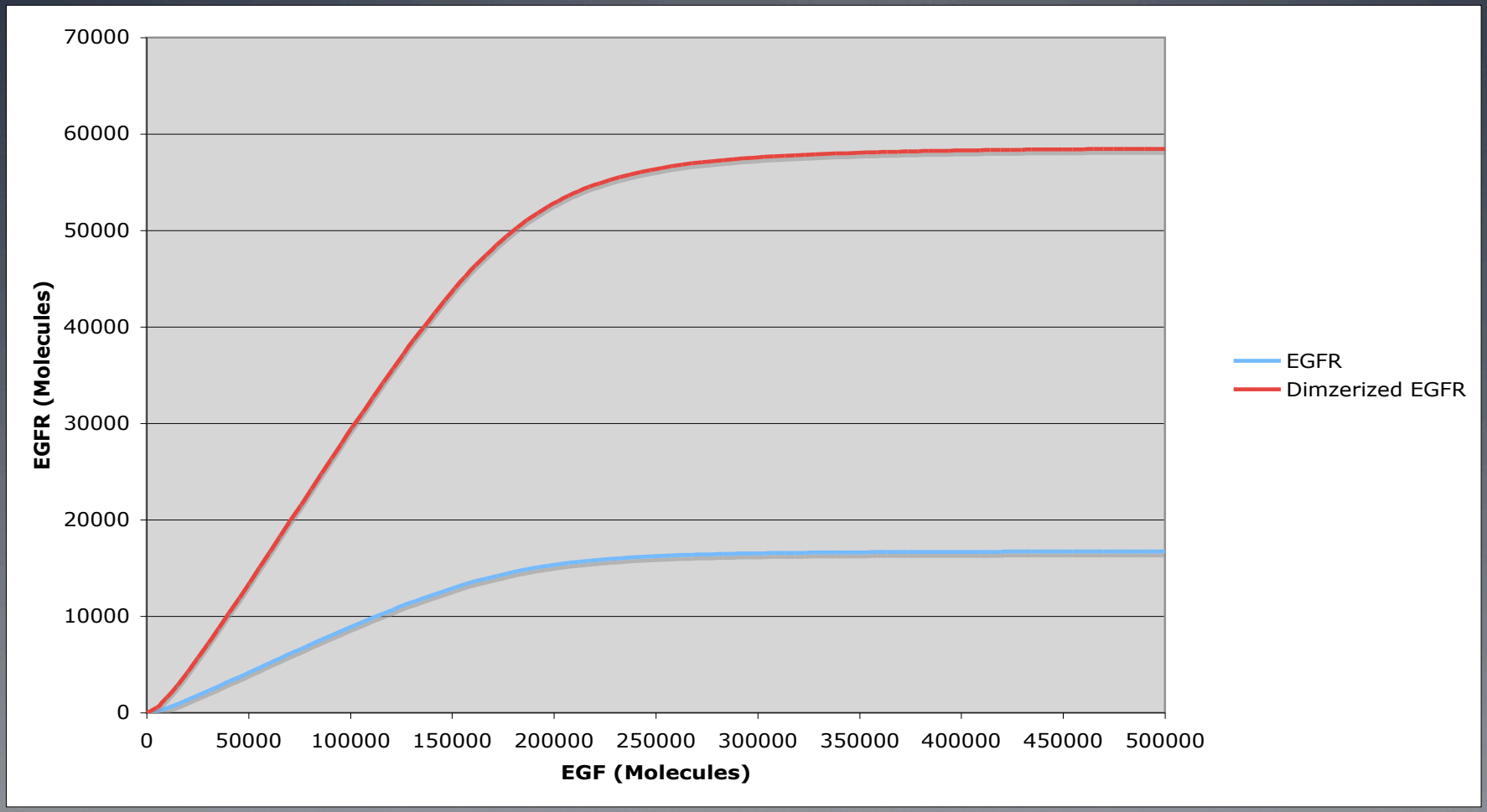
- Molecule Type: Null()
- Parameter: deg
- Rxn Rule:
  - Large: egfr() -> Null() deg DeleteMolecules
  - Small: EGF(R!1).EGF(R!2).EGFR(L!1,CR1!3).EGFR(L!2,CR1!3) -> Null() deg DeleteMolecules

EGFR Degradation

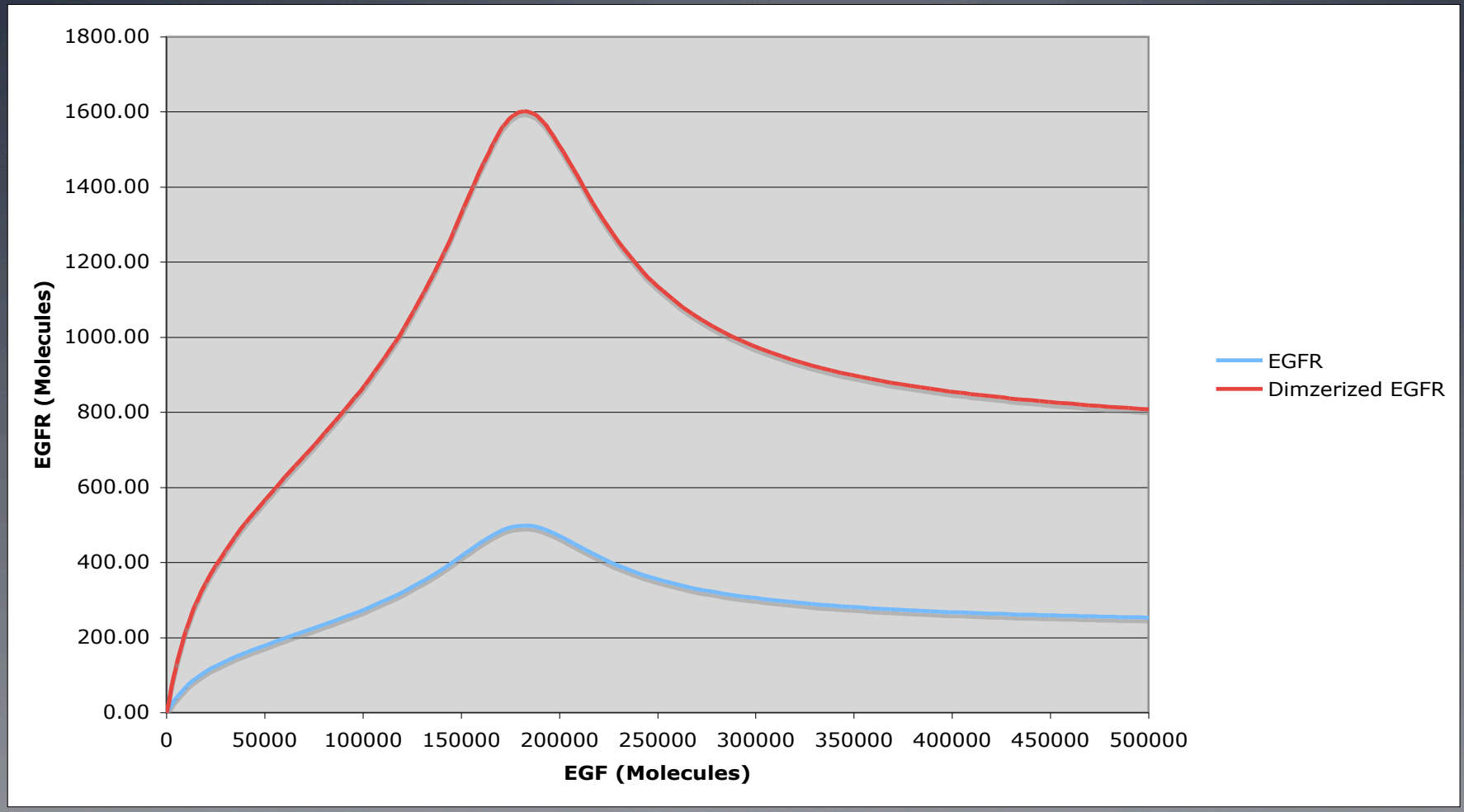
- In the small model as EGF increased the amount of EGFR did not increase as expected.

- Past some time point, the longevity of EFGR dimer maximizes at receptor saturation (180,000 molecules of EGF/ EGFR).

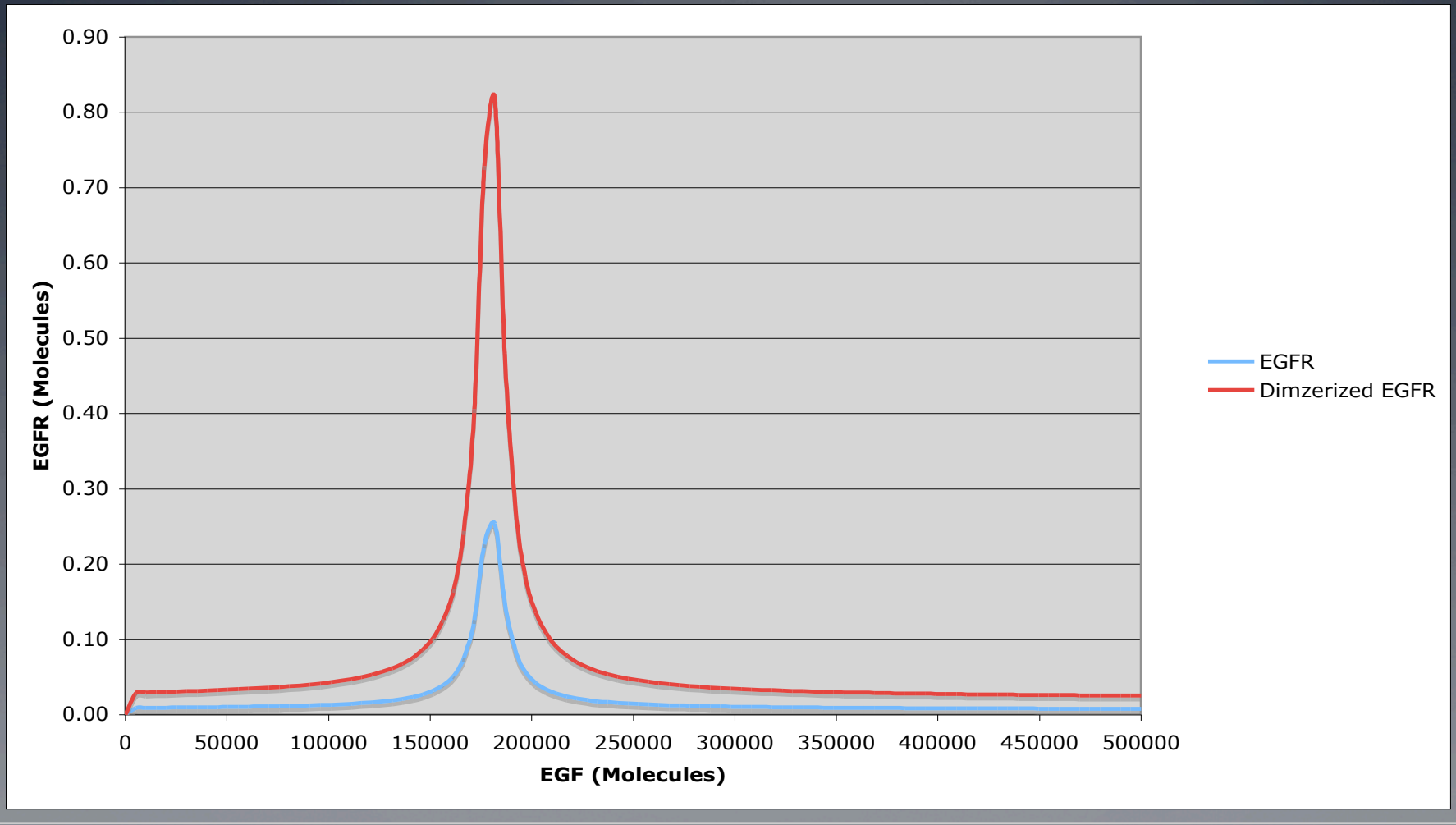
EGFR at 100 Seconds (Small Model)



EGFR at 1000 Seconds (Small Model)



EGFR at 10,000 Seconds (Small Model)



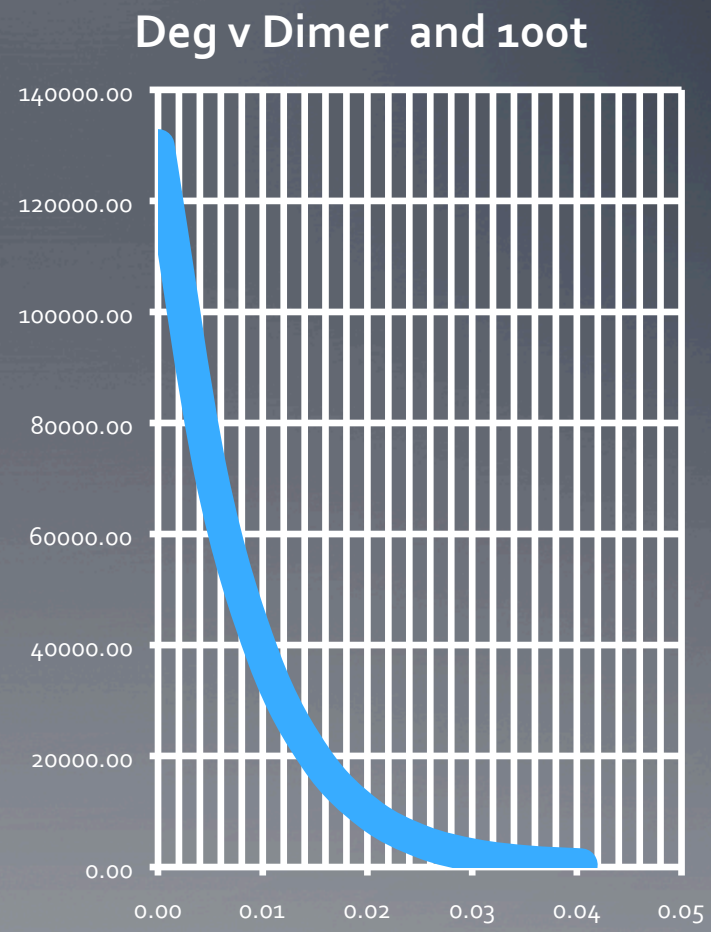
EGFR Small Vs. Large

- This optimal EGF rate raised some interesting questions:
  - Was this the result of the properties of the small model?
  - Could we reproduce the results in the large model?

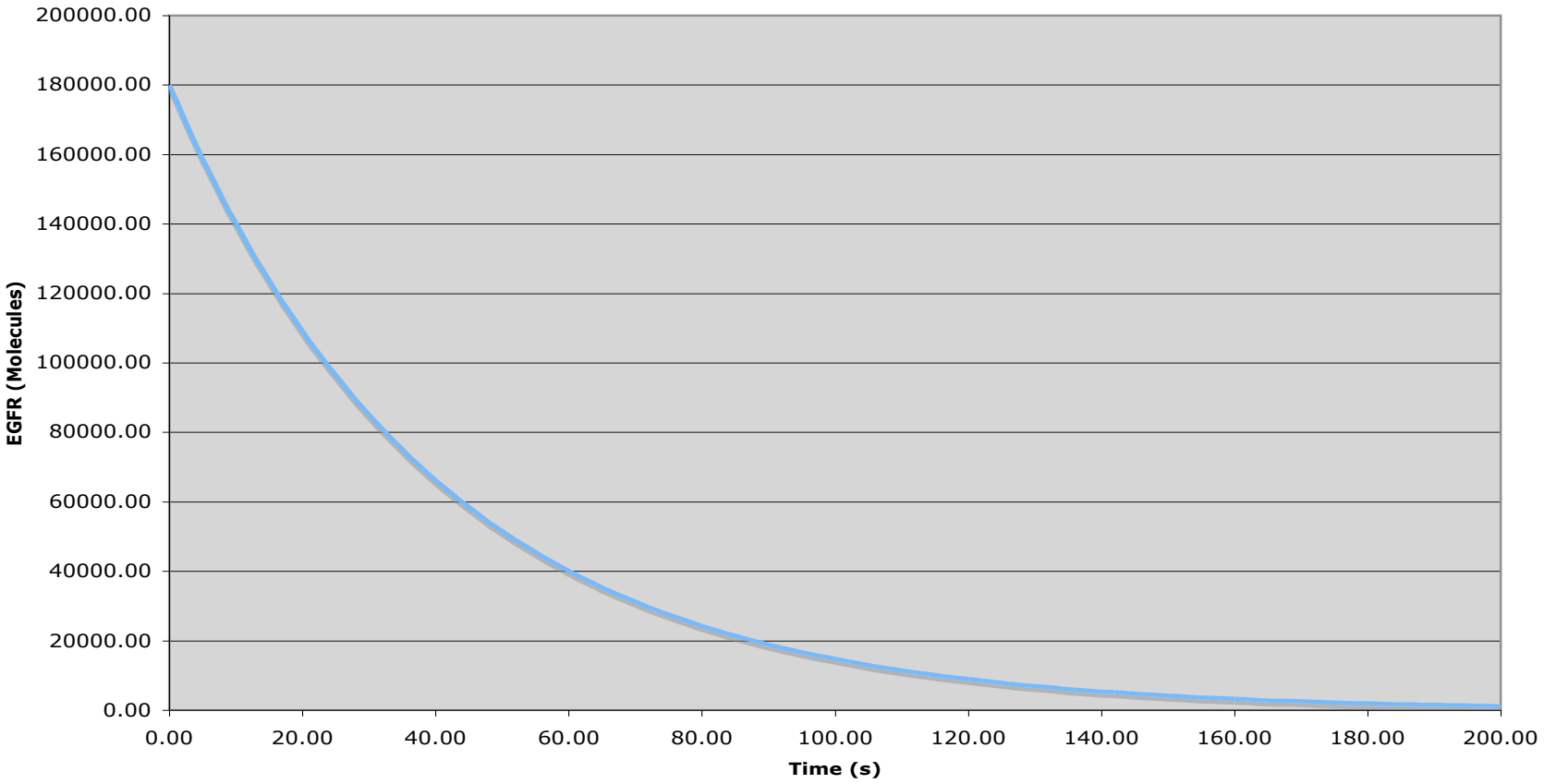
- Degradation differed between models.
  - Small – Only dimers
  - Large – All EGFR. Changing degradation to only dimers did not change results.

Choosing a Value for deg

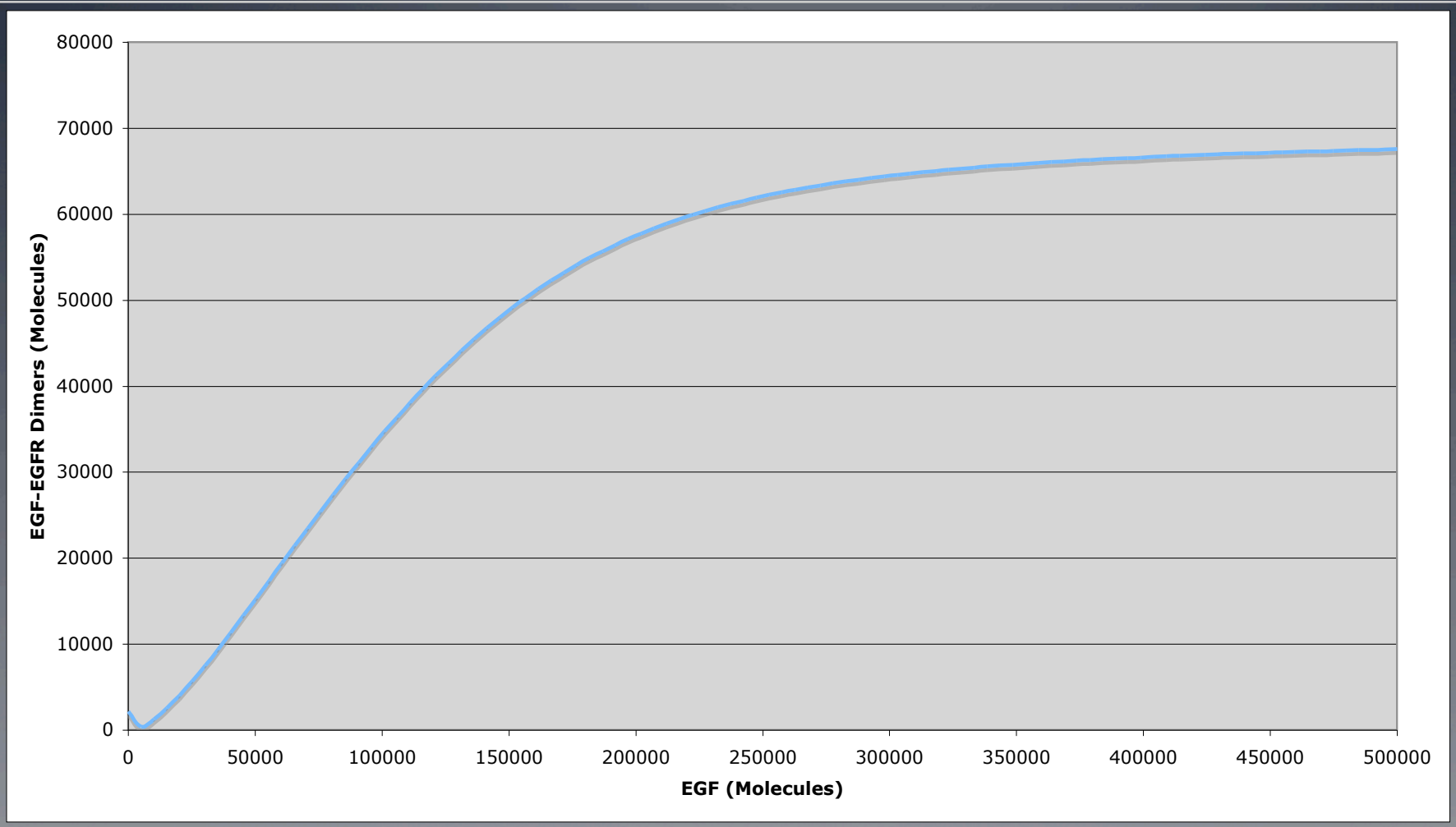
- At Time = 100, most of Dimer is degraded at deg = 0.025



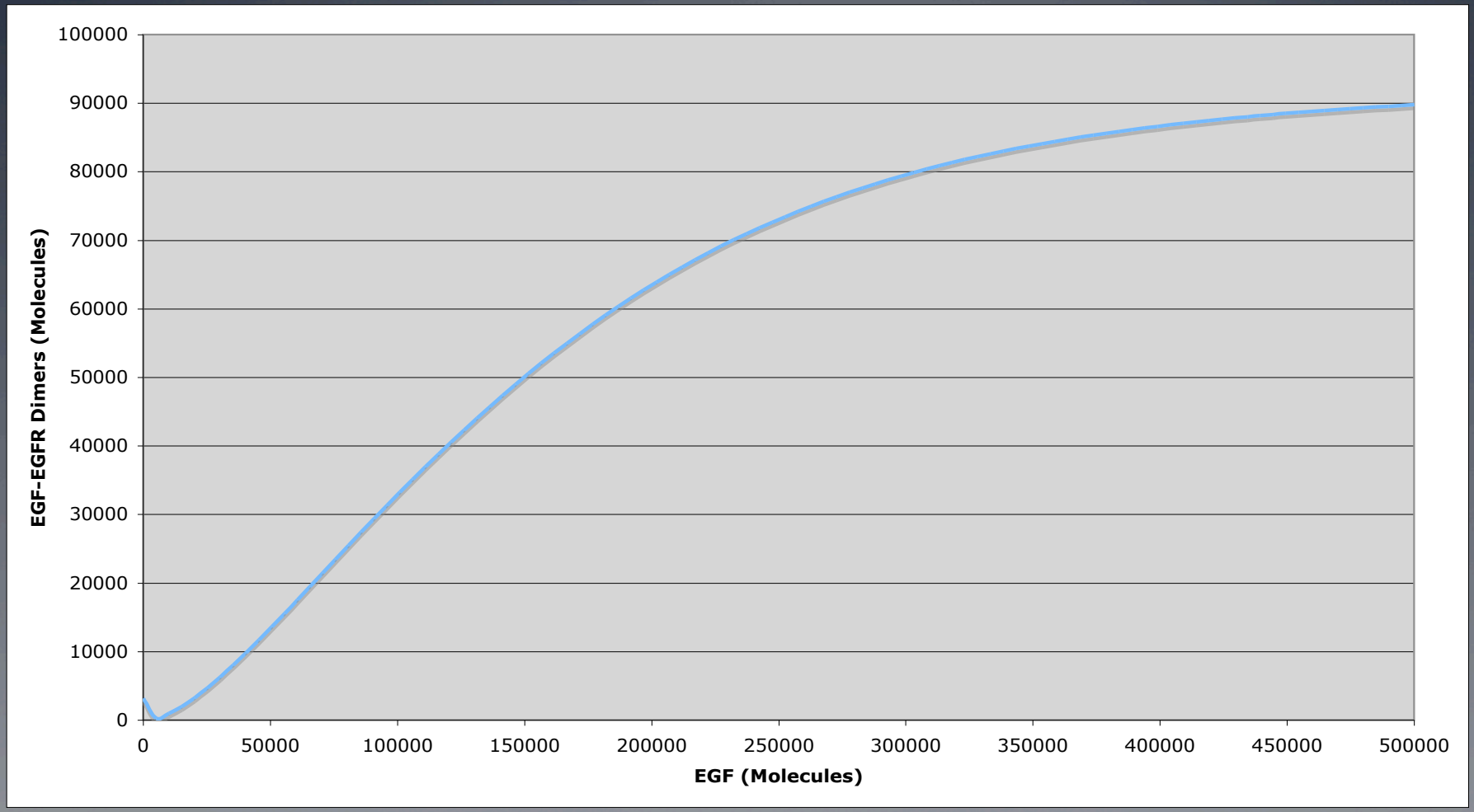
EGFR Degradation



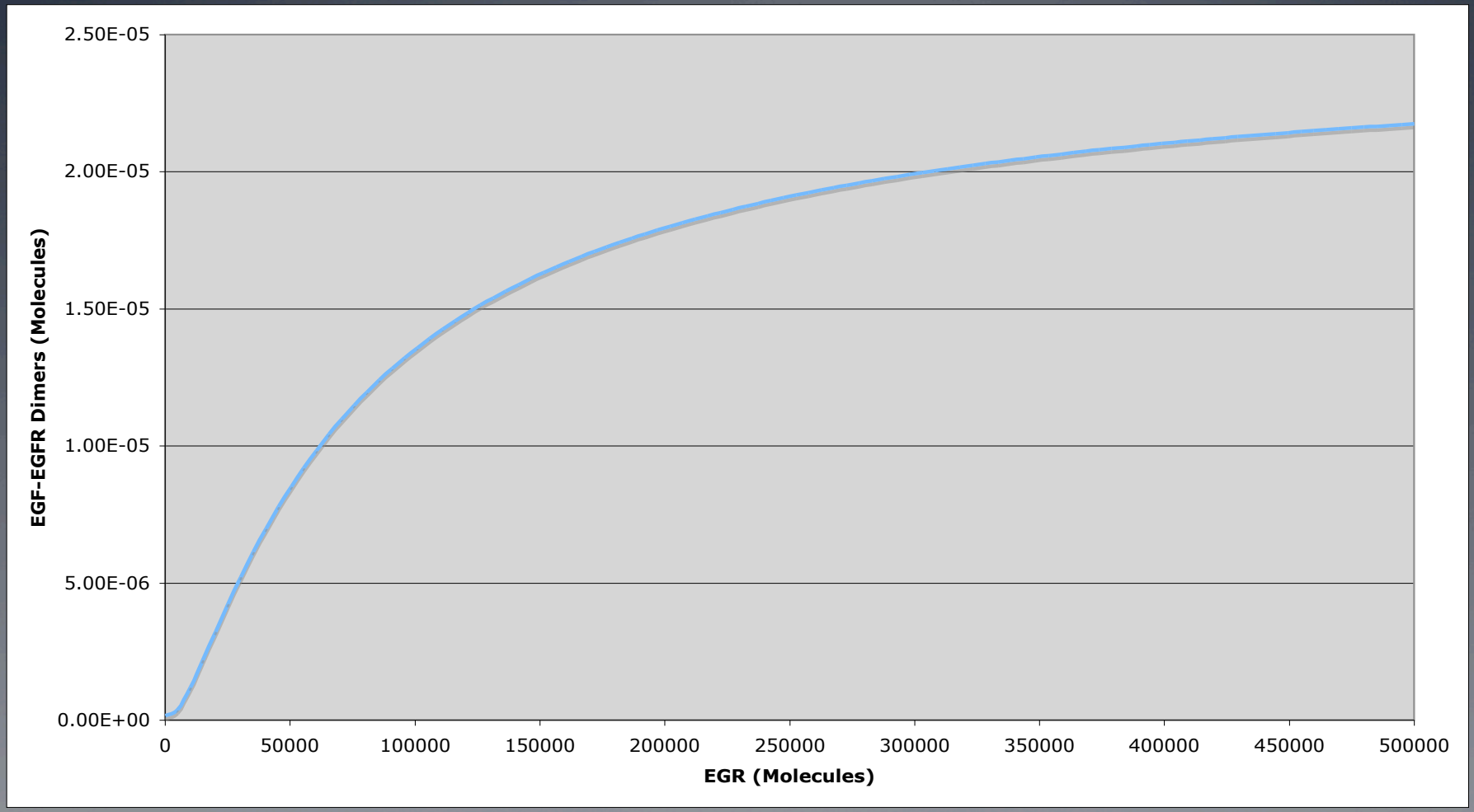
EGFR Dimers at 20 Seconds (Large Model)



EGFR Dimers at 100 Seconds (Large Model)



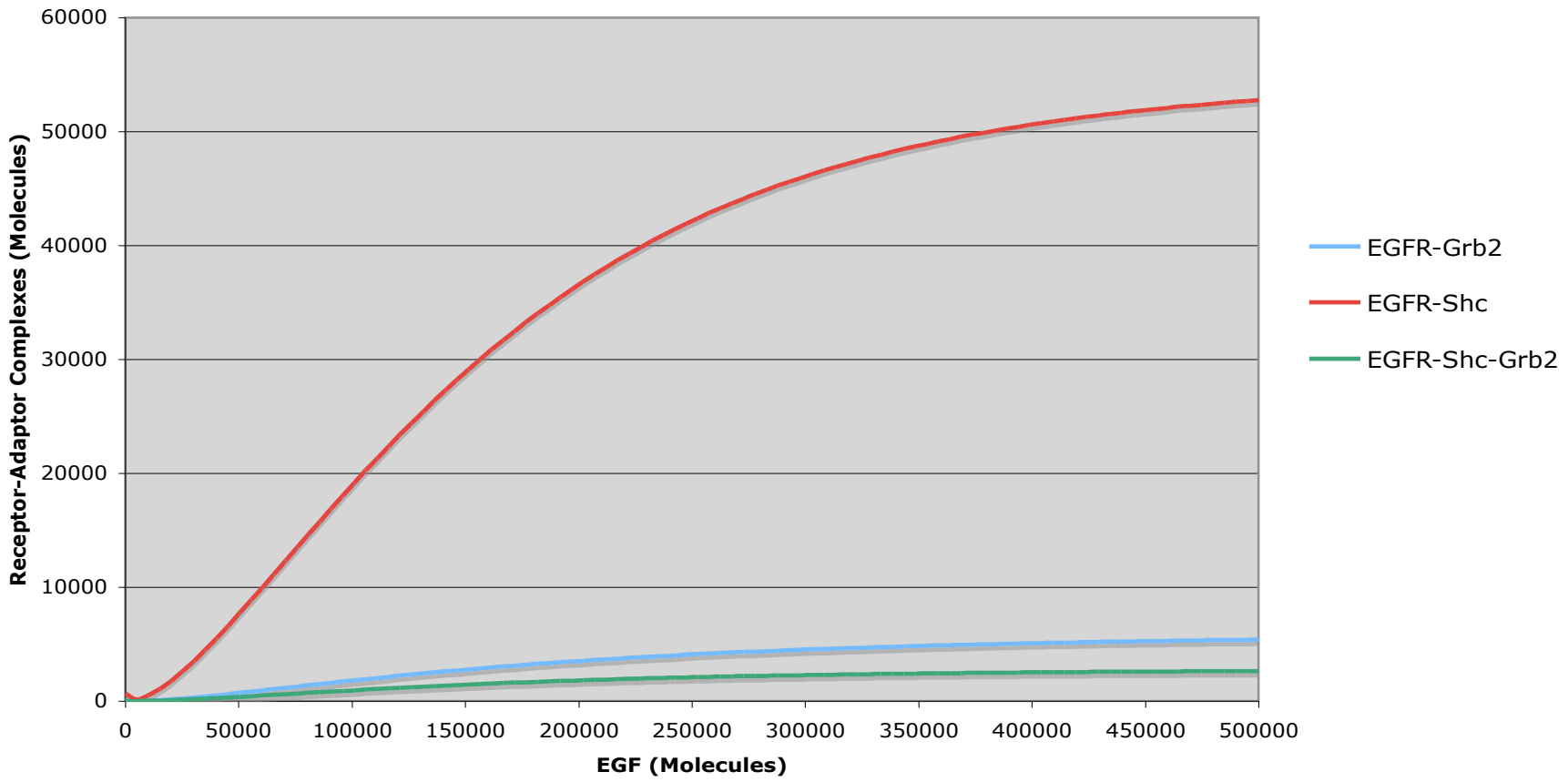
EGFR Dimers at 500 Seconds (Large Model)



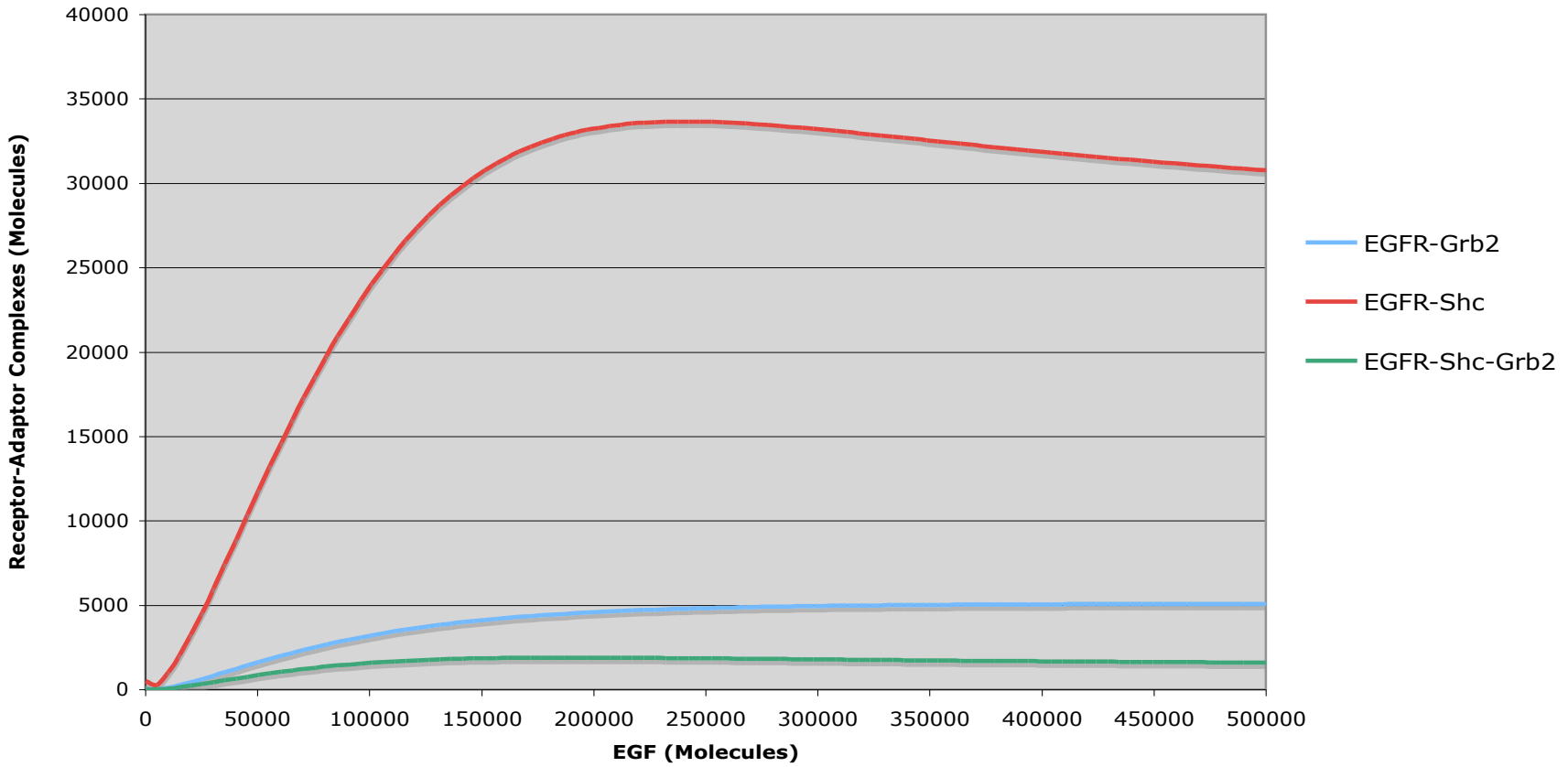
EGFR-Adaptor Bindings

- Parameter scan of EGF
  - Recall, EGFR increases as EGF increases.
- Parameter scans at t = 10, 20, 50, 100, 500, 1000

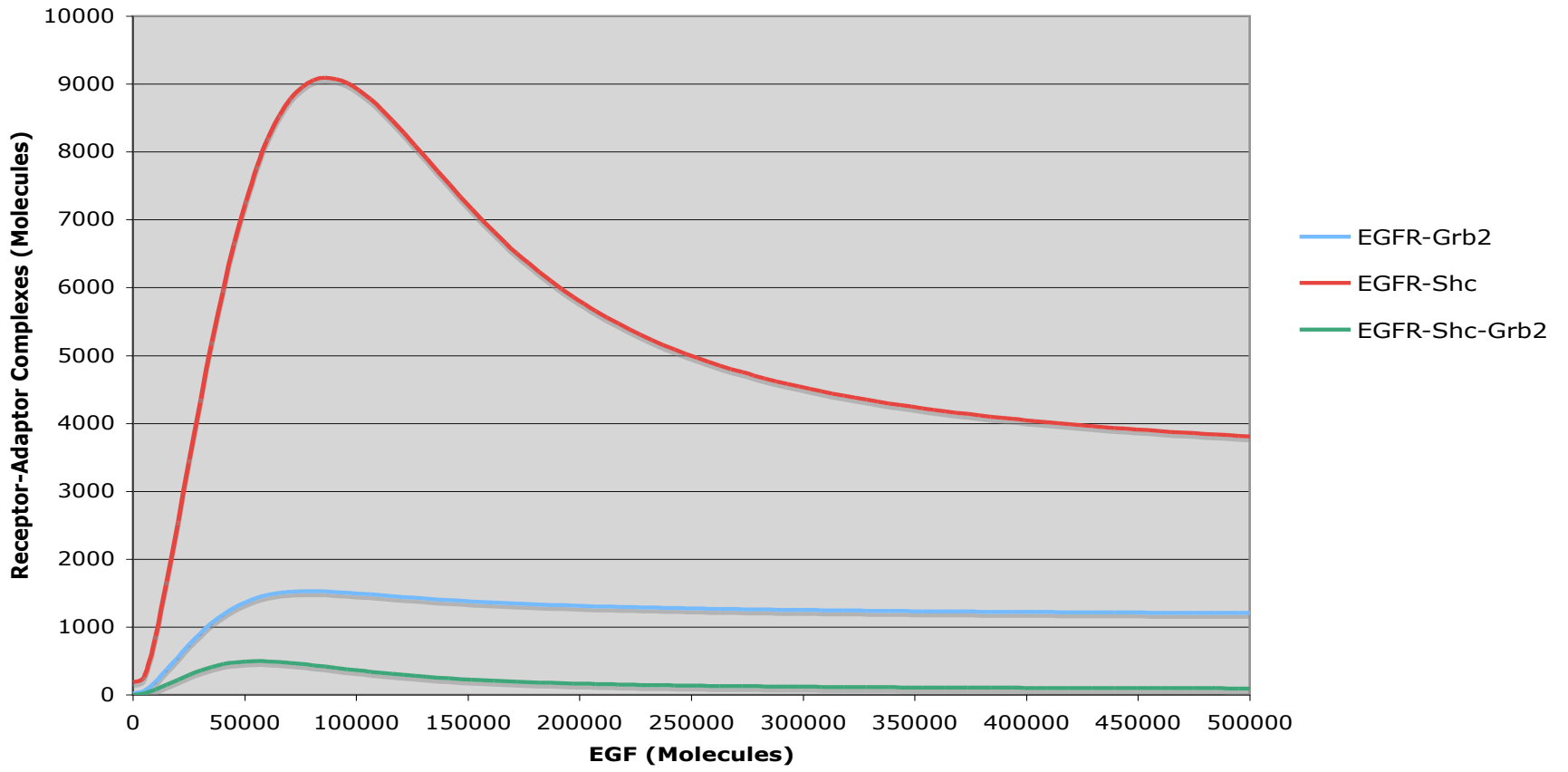
EGFR-Adaptor Bindings at 10 Seconds



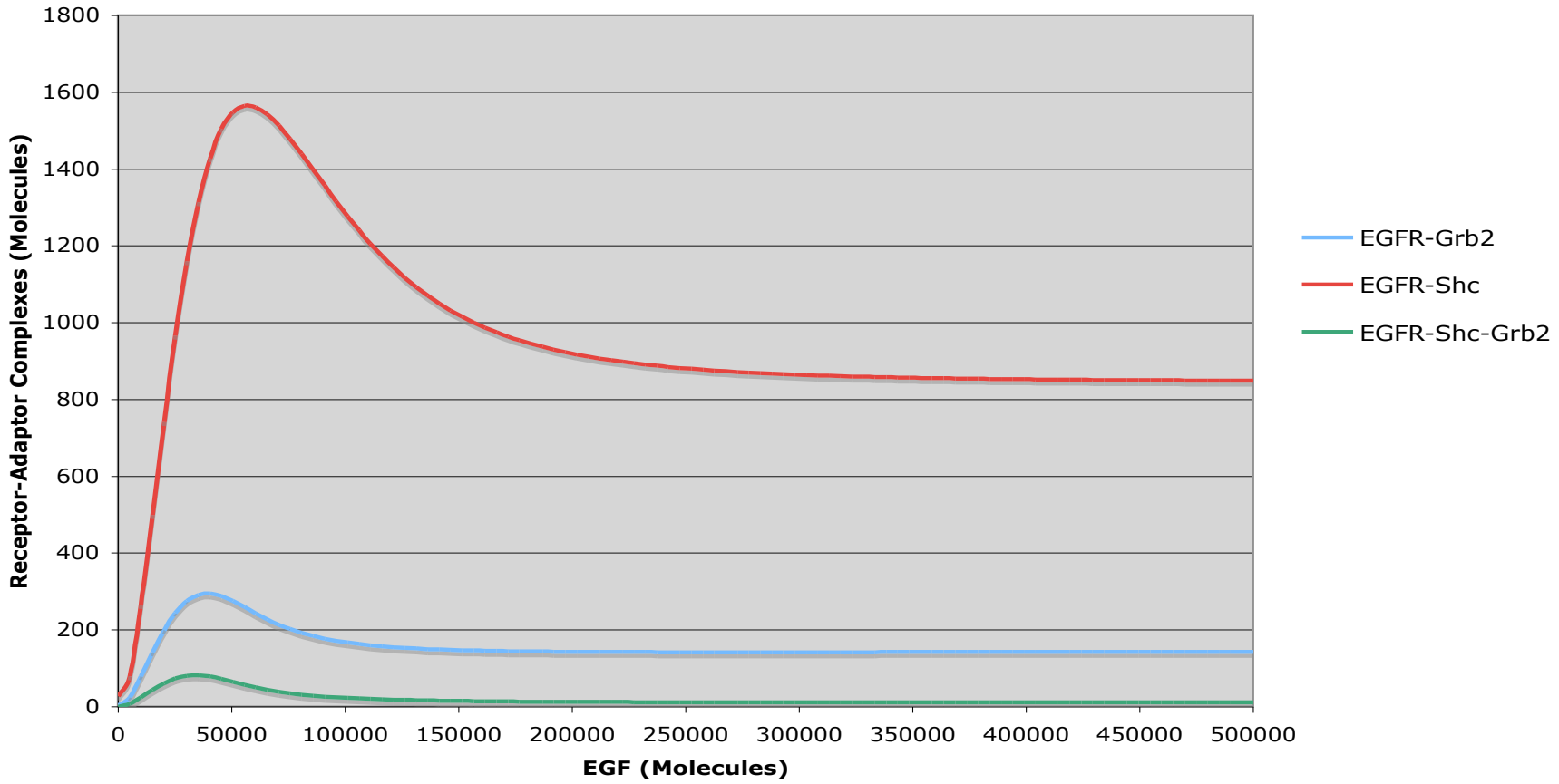
EGFR-Adaptor Bindings at 20 Seconds



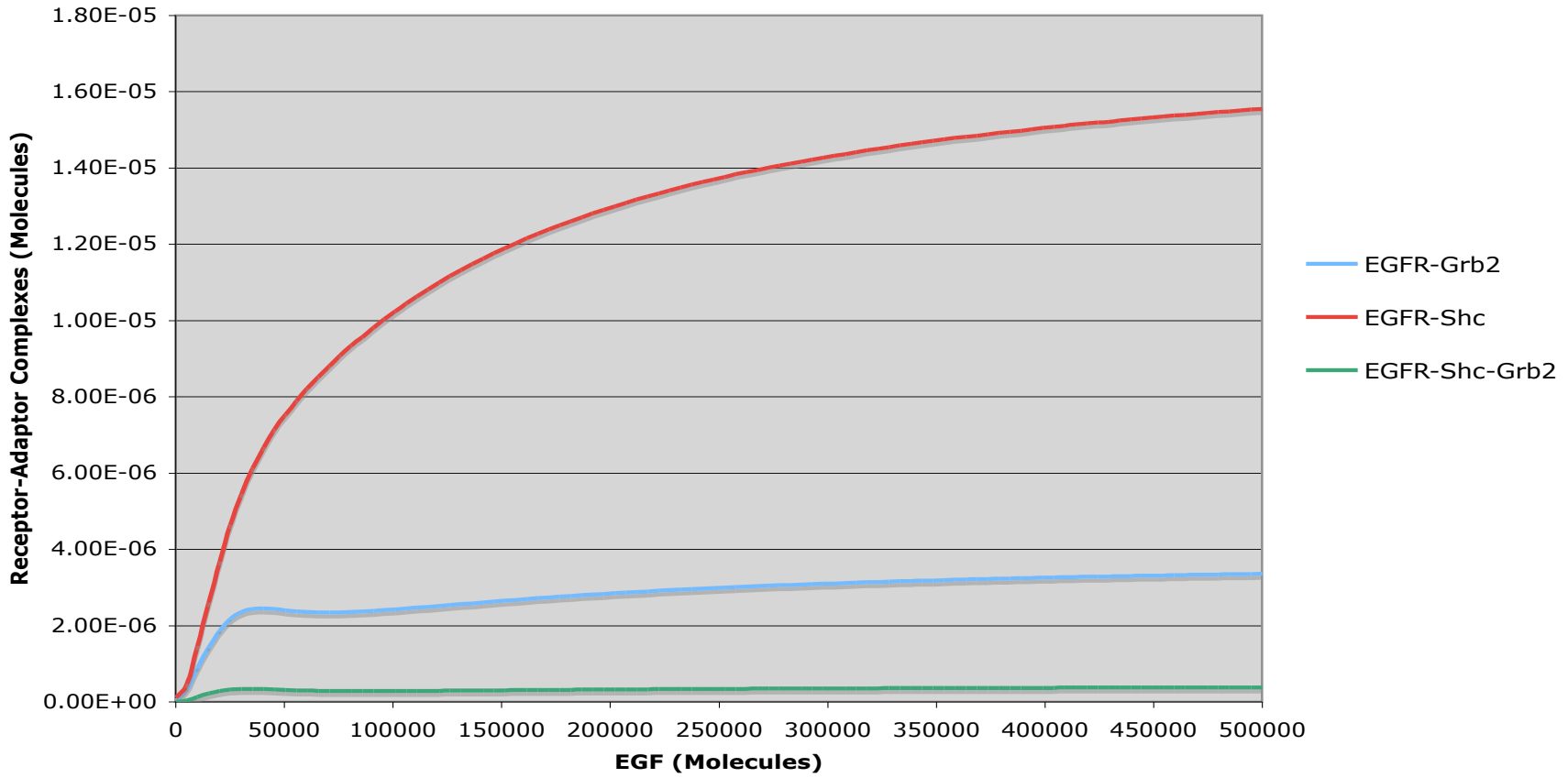
EGFR-Adaptor Bindings at 50 Seconds



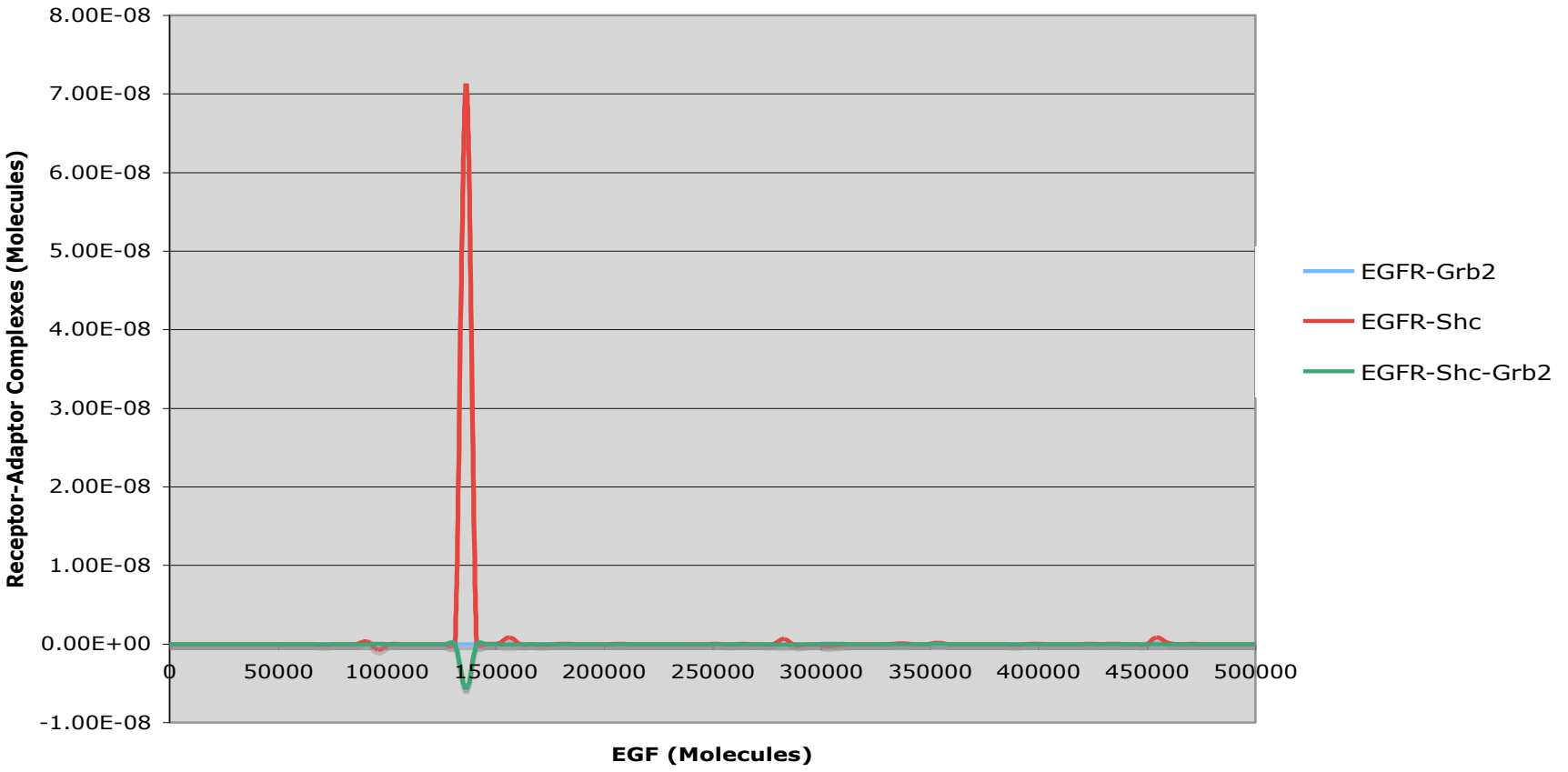
EGFR-Adaptor Bindings at 100 Seconds



EGFR-Adaptor Bindings at 500 Seconds



EGFR-Adaptor Bindings at 1000 Seconds



EGFR-Adaptor Bindings

- At each time point there is an optimal amount of EGF leading to stability.

- Also, a steady state appears past a critical EGF threshold.

Highlights

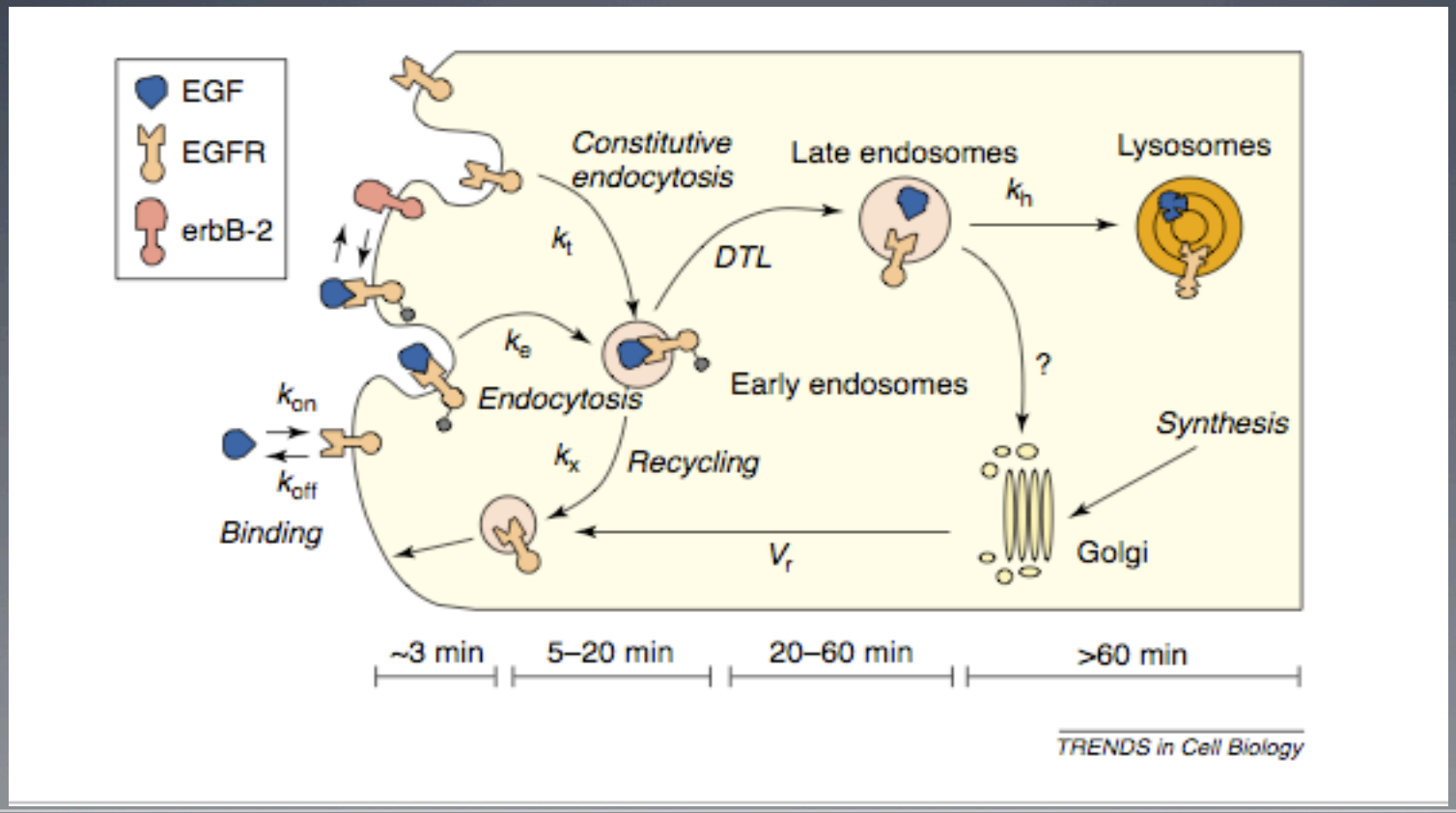
- Appearance of optimal EGF concentration near 180k inaccurate result of small model
- EGFR degrades as expected
- Dimer and receptor lifetime increases in proportion to EGF
- EGFR-Adaptor binding occurs at a optimal EGF concentration which itself is a function of time

Highlights

- Shc Vs. Grb2 time delay?
- Small Vs. Large optimal dimer stabilization
  - Is there a single reaction rule that destroys this effect?

Future Experiments

How can we make this model more biologically realistic?



Wiley SH et al, P 44 Fig 1

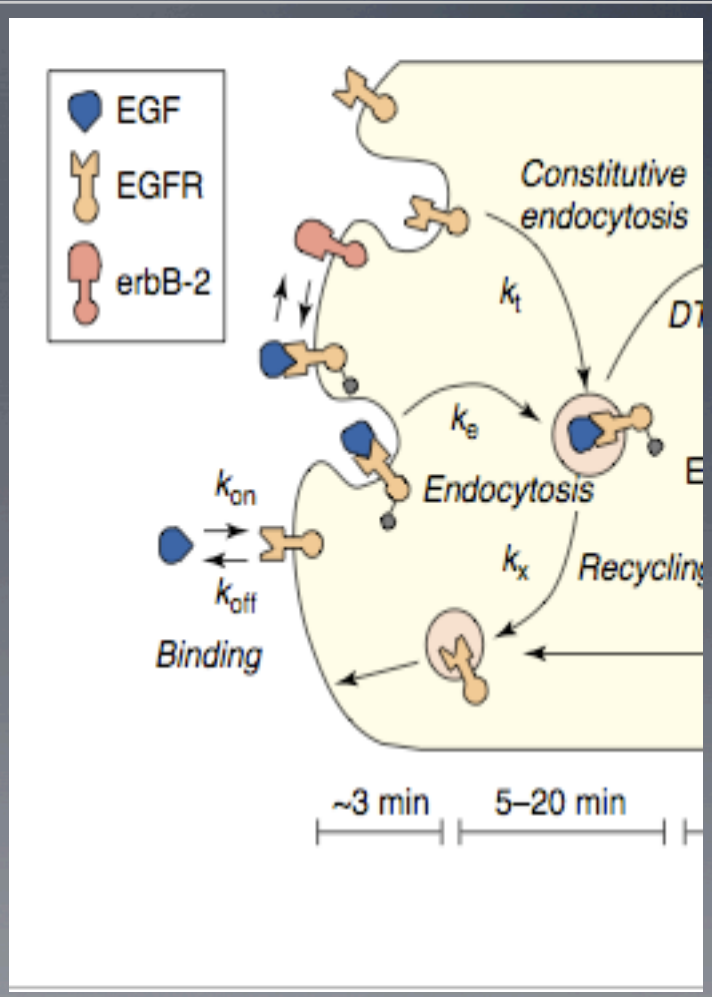
Differential Rates of Internalization

- Constitutive Endocytosis

  EGFR is constantly internalized at a steady rate

- Occupancy Induced Endocytosis

  Ligand bound EGFR is internalized at a higher rate



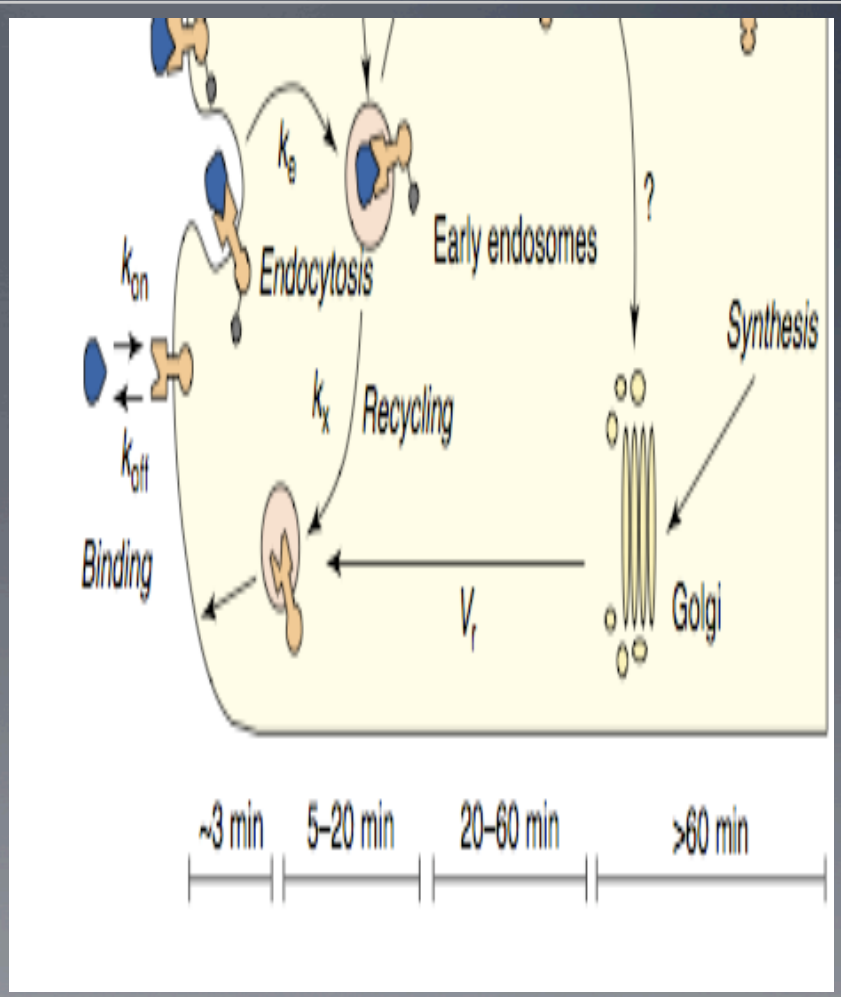
EGFR Migration to Membrane

- EGFR recycling

  EGFR from membrane can be recycled back to membrane

- EGFR production

  Newly translated EGFR finds its way to the membrane

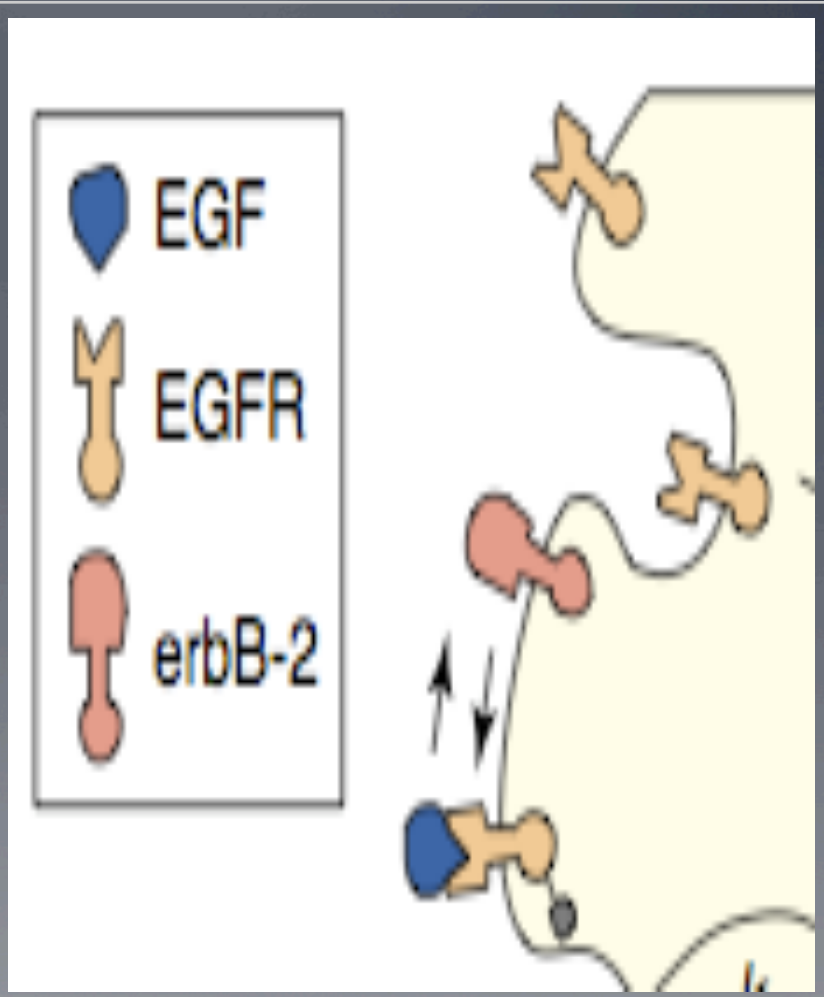


Heterodimerization and Trafficking Feedback

- EGFR can bind to other tyrosine kinase receptors, such as ErbB-2

  Experimentally shown that EGFR-ErbB-2 heterodimer internalization increases EGFR activity

- How does the state of internalized EGFR affect cell response?



References

- Wiley, S.H. et al. (2003) Computational modeling of the EGF-receptor system: a paradigm for systems biology. *Trends Cell Bio. 13, 43-50*