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# A Comparison of System Dynamics and Agent-Based SimulationApplied to the Study of Cellular Receptor Dynamics

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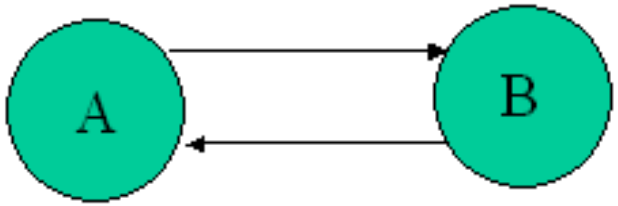
# The Questions

- Cellular receptor dynamics are analyzed via differential equations
- Thus, system dynamics (SD) is an obvious candidate methodology
- **But how well does SD "fit" the needs of a biomedical researcher?**
- **When might it be useful to model the phenomena at a biomolecular level?**
- **Will unexpected behavior modes emerge when concentrations and reaction probabilities are low?**
- **If so, would the use of agent based simulation (ABS) lead to new insights?**

# Approach & Findings

- We applied both SD and ABS to the study of non-equilibrium ligand-receptor dynamics
  - Over a broad range of concentrations
  - And, where the probability of interaction is varied from low to very low
- We found that both approaches offer much to the researcher and are complementary
- We did not find a clear demarcation indicating when one paradigm or the other would be strongly preferred

# A seemingly trivial starting point




- Receptors are in one of two states, {A} and {B}
- Over time, receptors in state {A} shift to state {B}
  - e.g. they become “bound”
- Similarly, receptors in state {B} shift [back] to state {A}
- Simple 1st order dynamics
  - The quantity in each state always approaches an equilibrium
  - The time to reach equilibrium and the final fraction in a each state depends on the forward and reverse reaction probabilities
- This is, of course, easily modeled via SD

# Notation & Basic Math

- k1_f_EFF = (1/mol-time) x ligand (mol) = 1/time

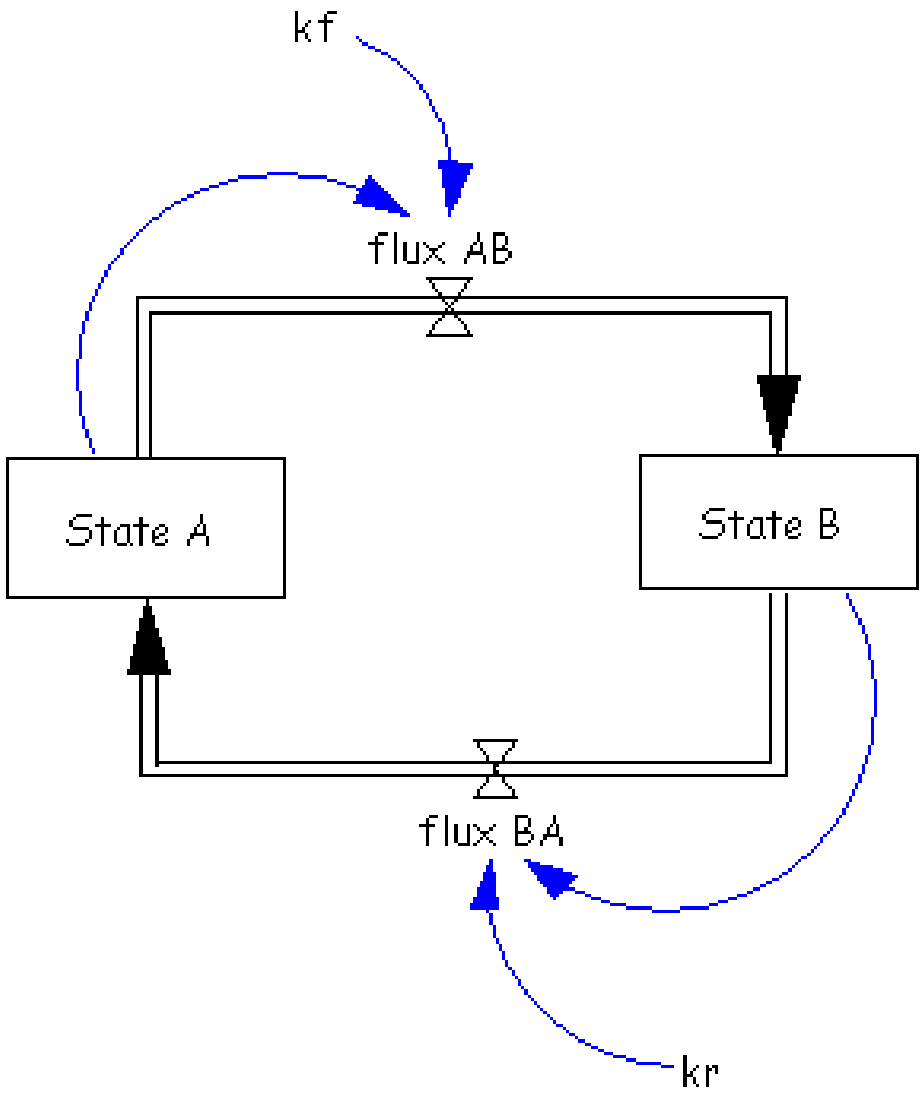
- LR_associations/time = R • k1_f_EFF
  - Assuming constant ligand concentration
  - Binding decreases as unbound receptor R is depleted.

- The LR complex also dissociates spontaneously
  - Again following first-order decay kinetics: k1_r = 1/time

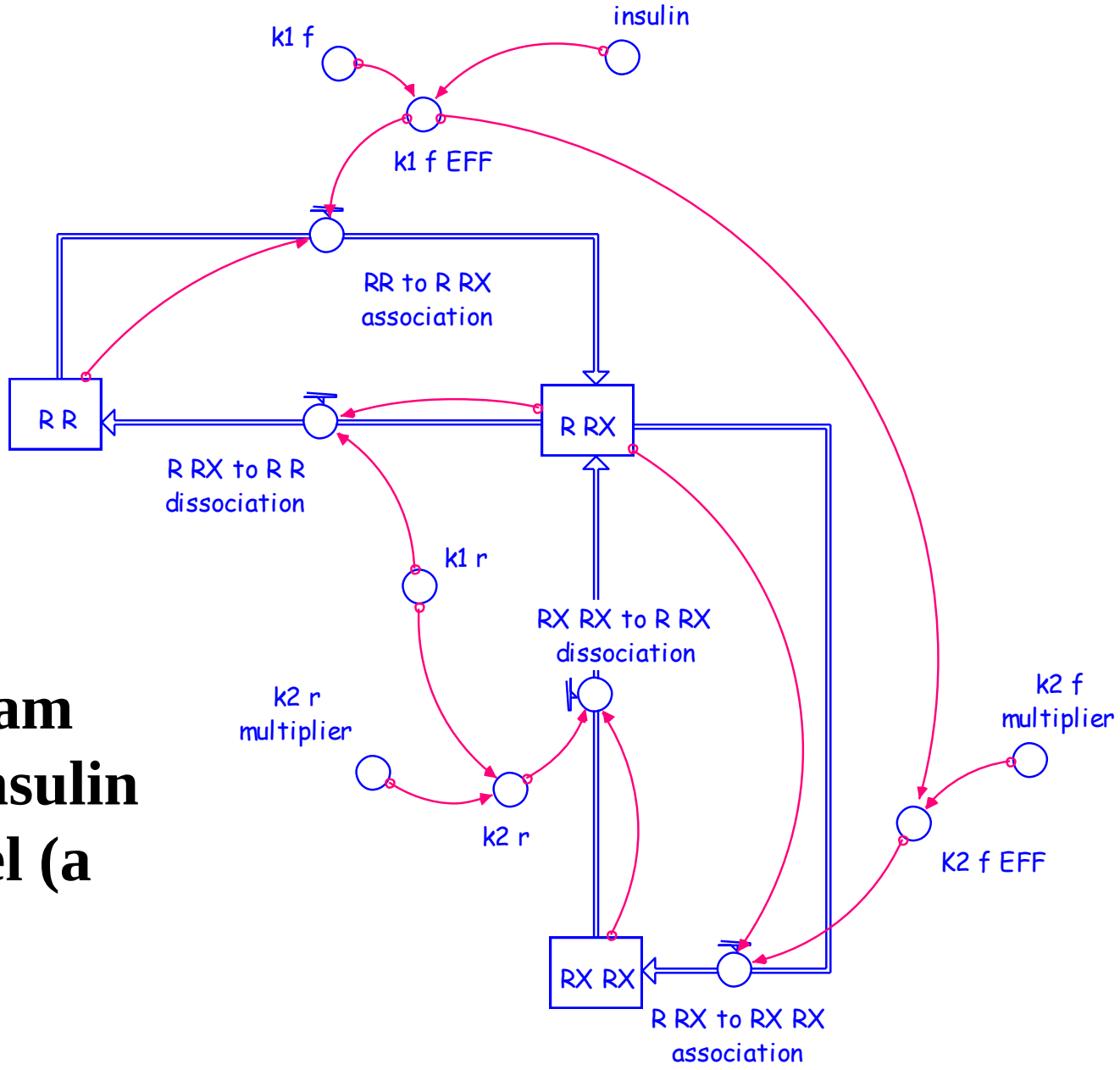
- LR_dissociations/time = LR • k1_r

- Bound R = ((Total R) * L) / ($K_D$ + L)

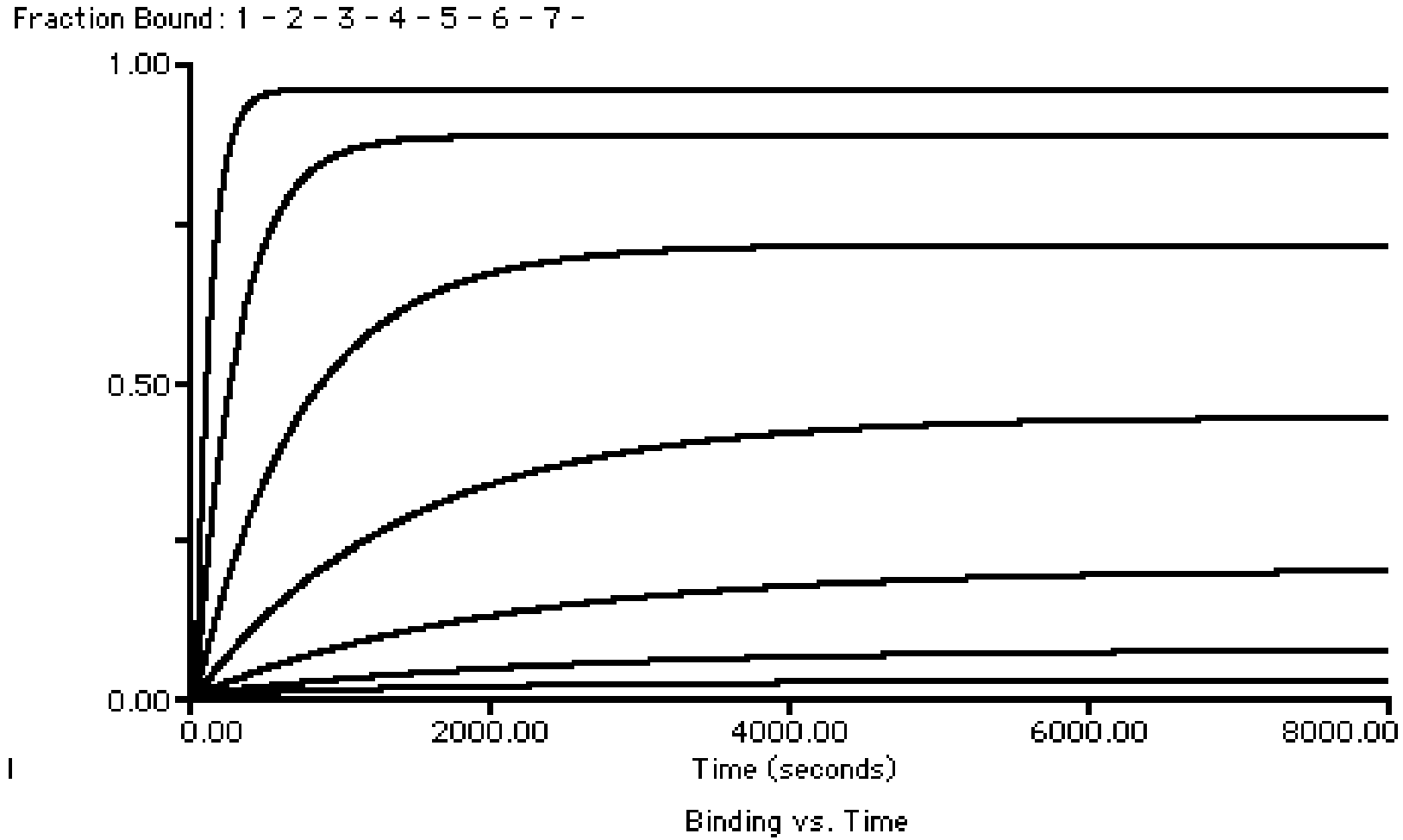
# SD Flow diagram for generic 2SE model



# SD flow diagram for Divalent insulin receptor model (a 3SE model)



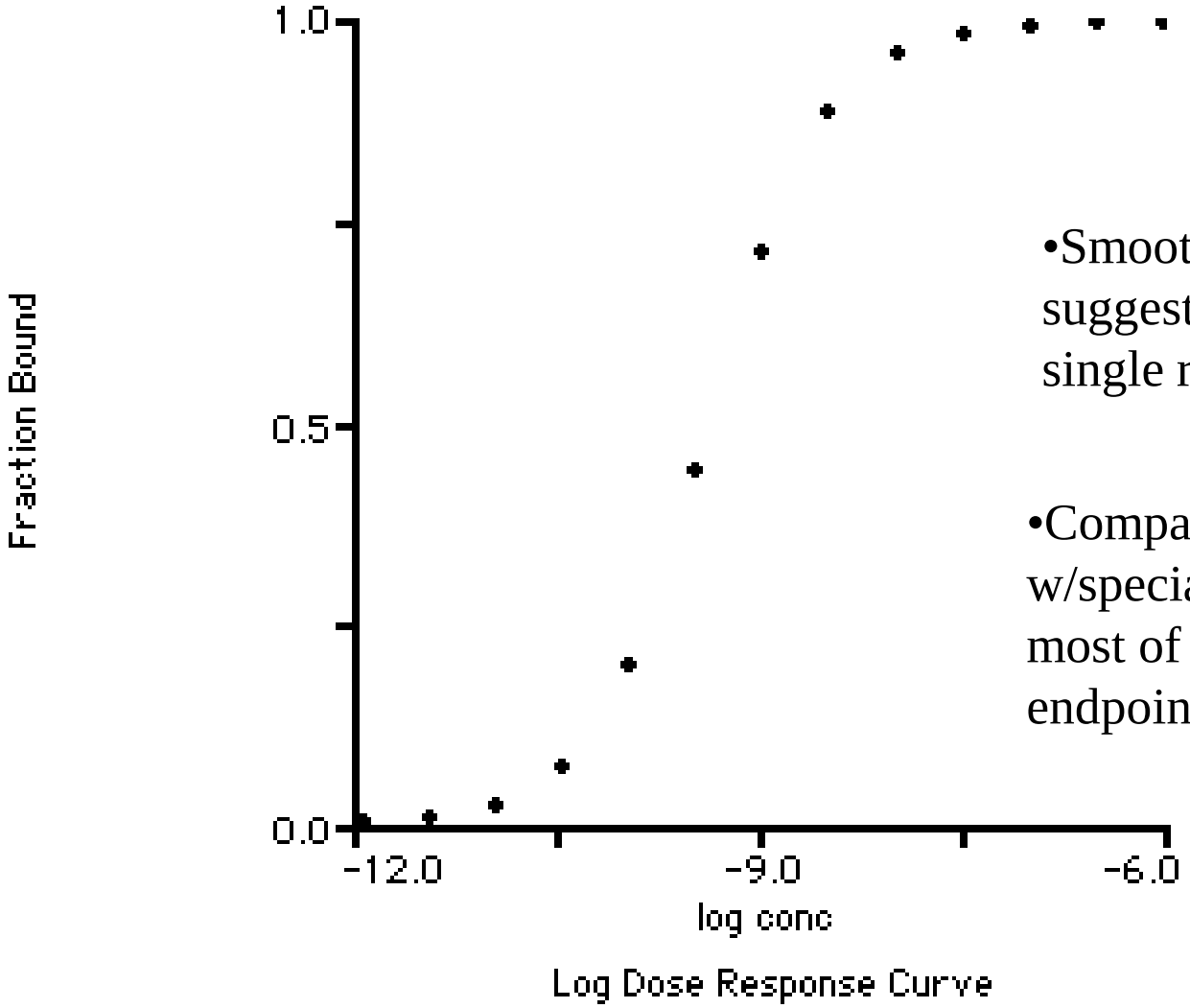
**Fraction bound over time with different ligand concentrations** (using sensitivity analysis feature)



# Different Types of Diagrams

- Plotting behavior over time is obviously easy
- But, can the SD model be used to create the types of diagrams used by biomedical researchers?
  - The log dose response curve?
  - The Scatchard plot?
- We felt that perhaps we could utilize the automated sensitivity analysis features to do so…

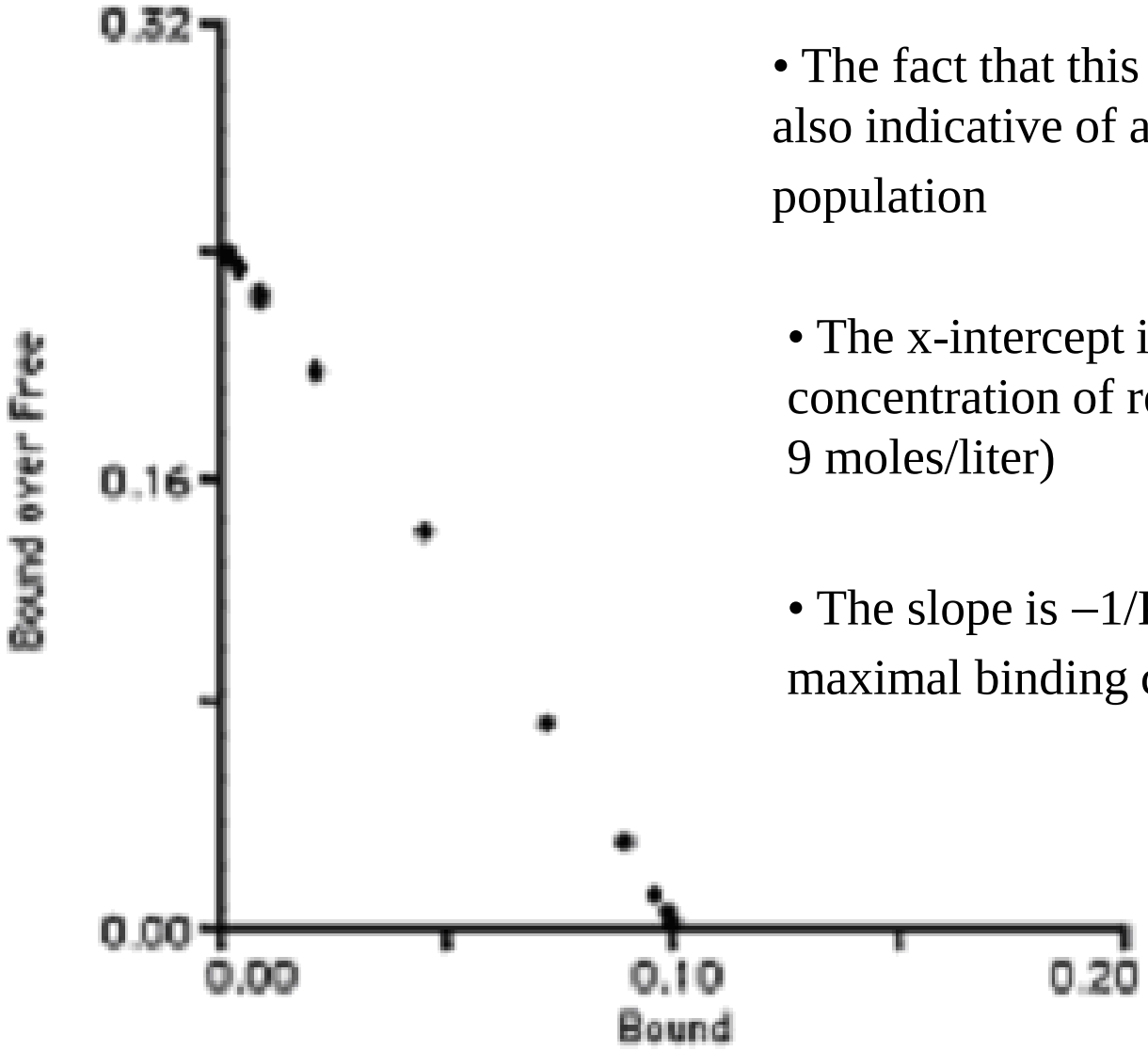
# Log dose-response curve




- Smooth sigmoid curve suggests the presence of a single receptor population

- Comparative x-y graphs w/special logic to suppress most of the trace so only the endpoints show

# The Scatchard Plot




- The fact that this plot is linear is also indicative of a single receptor population

- The x-intercept is the concentration of receptor (.1e-9 moles/liter)

- The slope is $-1/K_D$, the half-maximal binding concentration

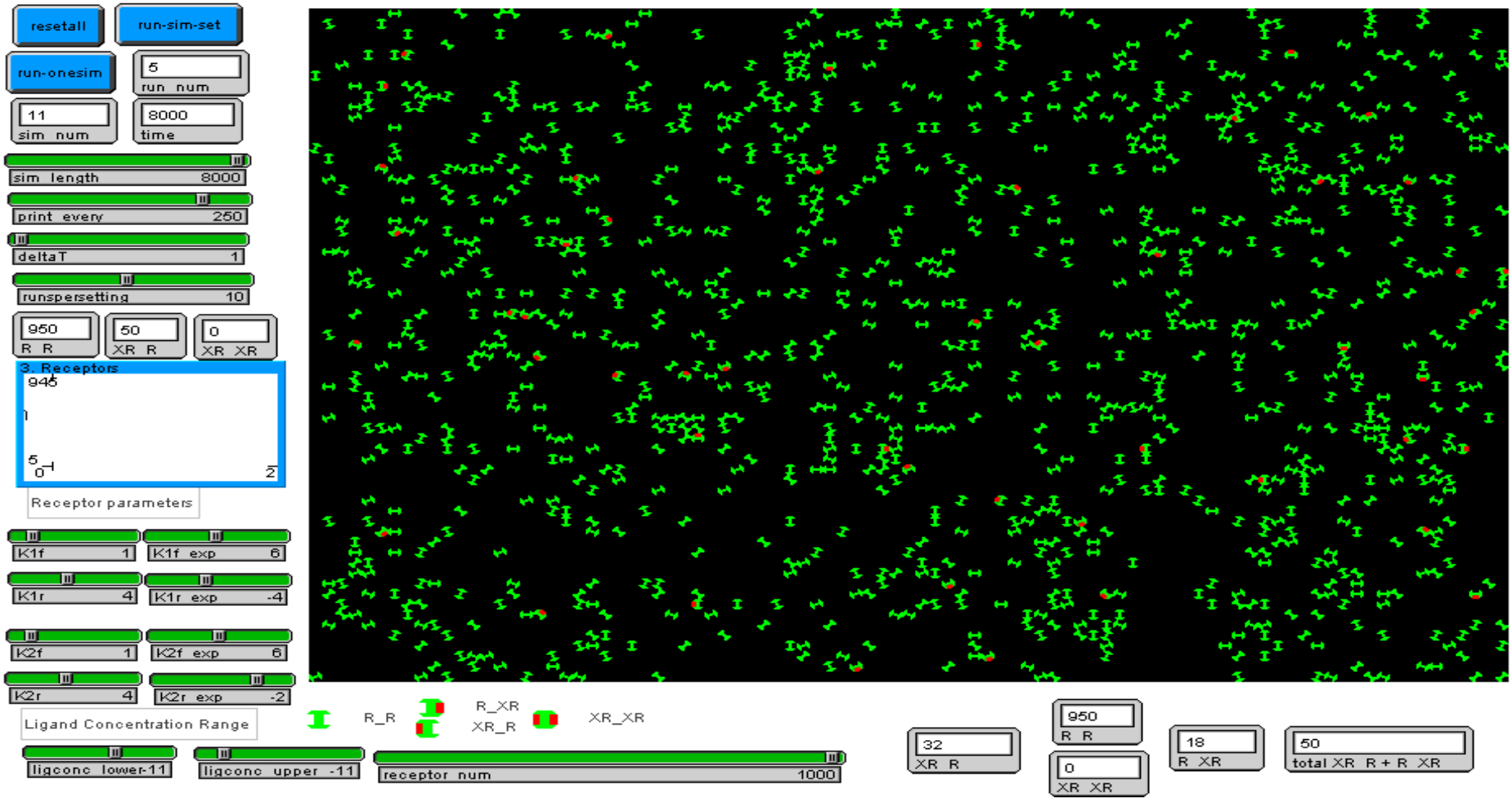
# Comments about SD Modeling

- SD model results match the literature
- SD is well suited to analyzing multi-state equilibrium processes
- SD can create the plots and charts used by biomedical researchers
- SD modeling can enhance the researchers' intuition regarding the underlying biological processes
  - Through the process of building SD models
  - By understanding the structural properties of these models
  - By experimenting with widely varying parameter values
- Thus, SD can help to enhance the researchers' ability to design and interpret laboratory experiments and experimental data

# So why bother with ABS?

- Would it be useful to model the phenomenon at the biomolecular level?
- With SD, the plots would all have the same "shape" regardless of the concentration
  - everything is simply "scaled"
- But, can studying the statistical variation that results at very low concentrations lead to useful new insights?

# An ABS Model (using StarLogo in this case)



# StarLogo code fragments from the divalent insulin receptor model

```
setsim_num 0
 setligconc (10 ^ ligconc_lower)
 calc-keffs
 setnumber_sims 4 * (ligconc_upper -
ligconc_lower) + 1
 repeat number_sims
  [
  setsim_num sim_num + 1
  setrun_num 0
  repeat runspersetting
   [
   setrun_num run_num + 1
   run-sim
   ]
  setligconc ligconc * (10 ^ .25)
  calc-keffs
```

An illustrative segment of the control logic for running experiments, potentially multiple times for a given ligand concentration

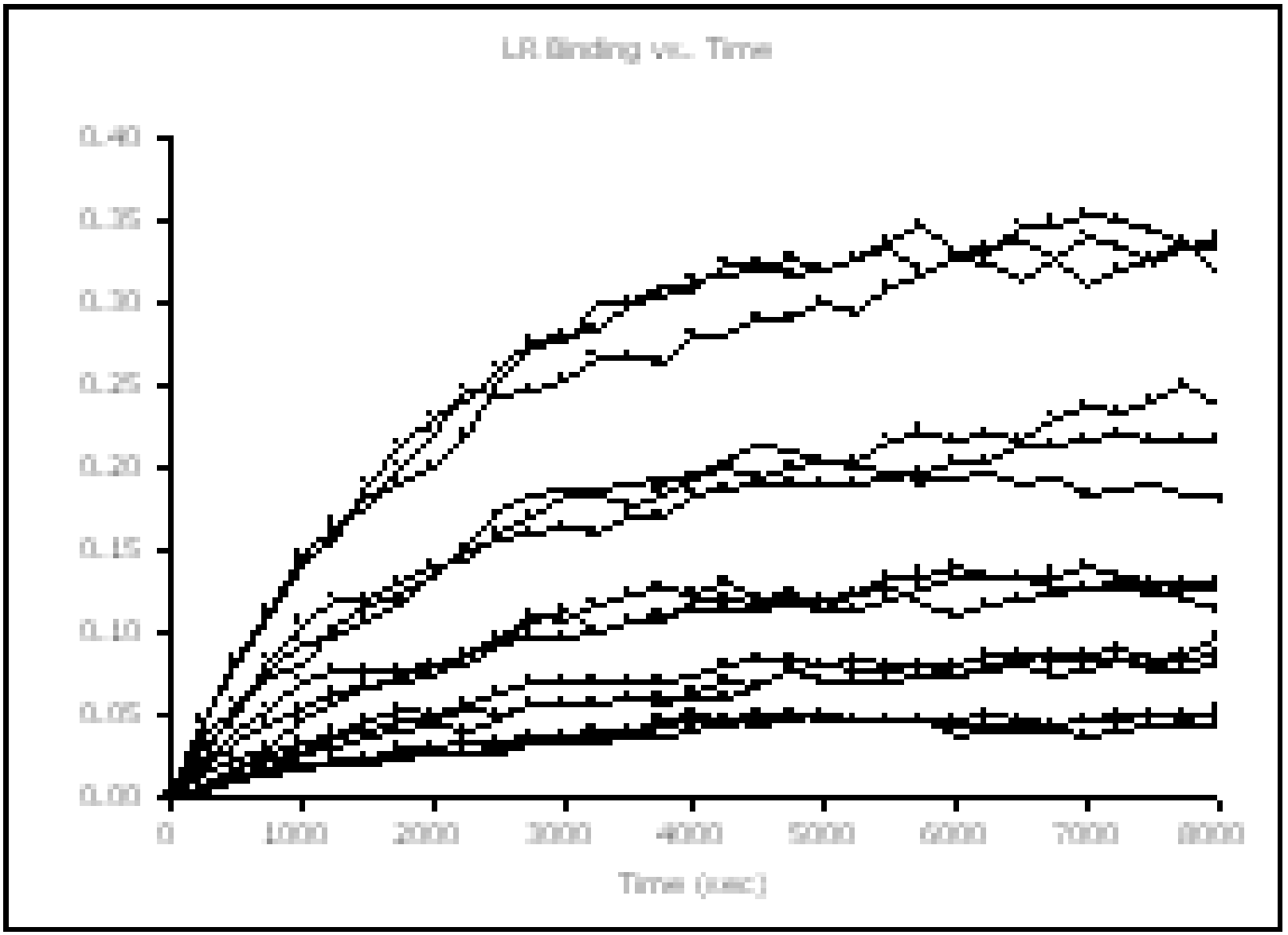
```
to calc-keffs
  setK1f_eff1000000 1000000 * 2 * ligconc
* K1f * (10 ^ K1f_exp) * deltaT
  setK2f_eff1000000 1000000 * ligconc *
K2f * (10 ^ K2f_exp) * deltaT
  setK1r1000000 1000000 * K1r * (10 ^
K1r_exp) * deltaT
  setK2r1000000 1000000 * 2 * K2r * (10 ^
K2r_exp) * deltaT
```

Logic to calculate the reaction constants for a given ligand concentration

```
To check-bind
 if (state = unbound)
  [
   if (random 1000000) < K1f_eff1000000
     [
      ifelse ((random 100) < 50)
        [setshape shape-R_XR]
        [setshape shape-XR_R]
      setstate bound
      setstate_num -1
```

A fragment of an agent procedure that determines if binding will occur, and if so, what happens

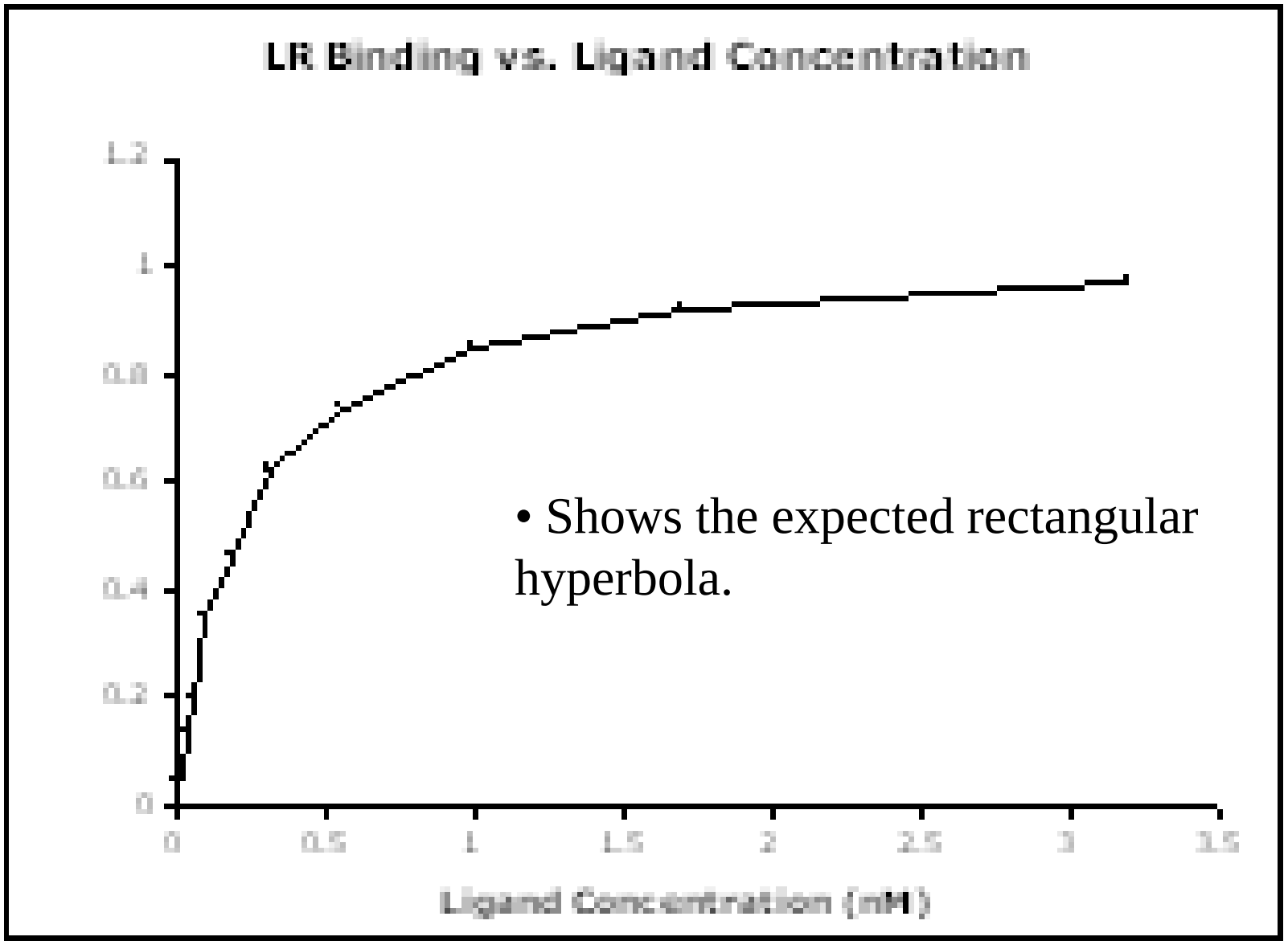
**Ligand-receptor binding vs. time** (N=1000, 3 runs/conc.)



# Lab notes regarding multiple model runs at low concentrations

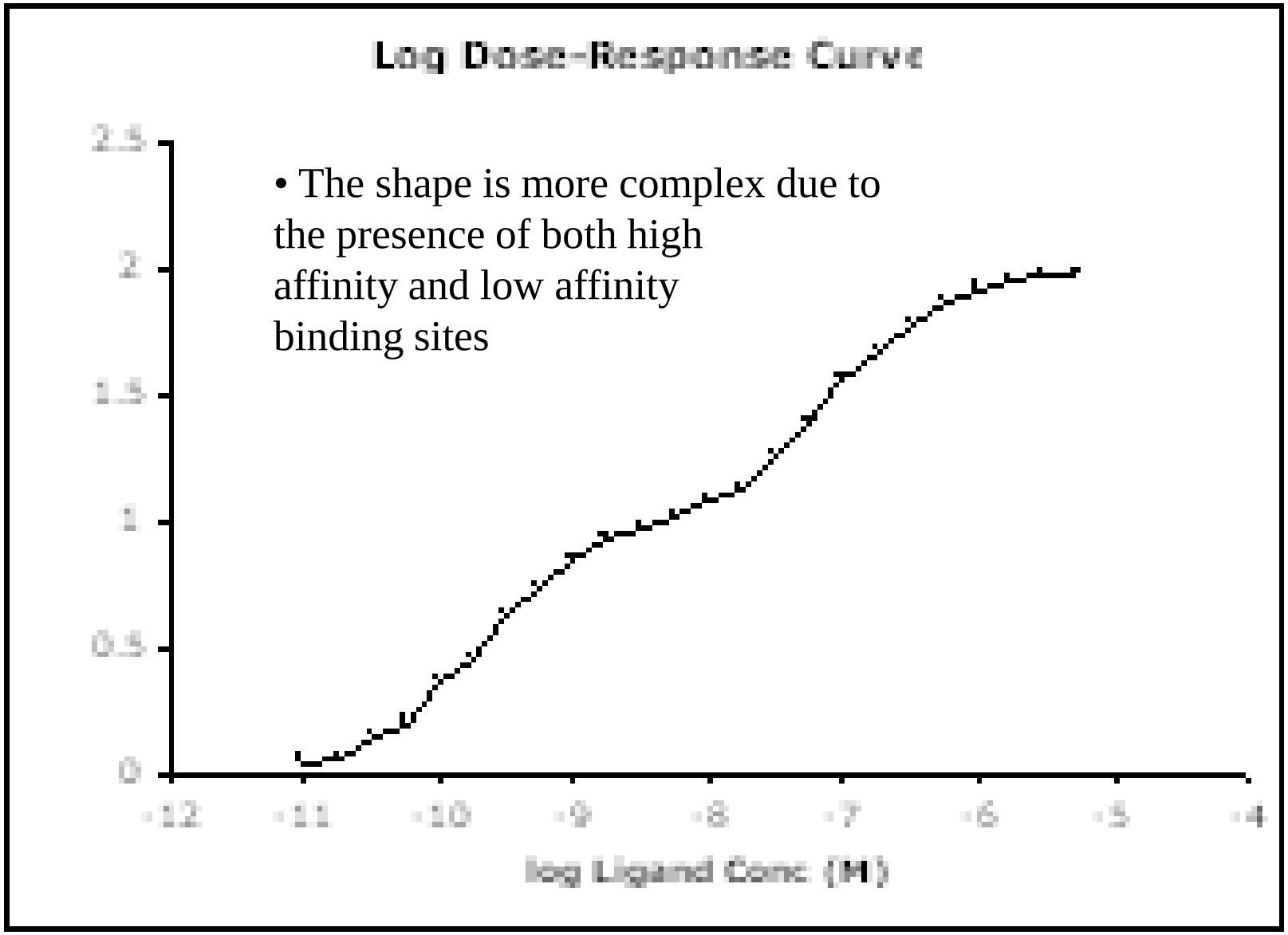
| | Final # Bound | | | | |
|---|---|---|---|---|---|
| Concen-tration | Run A | Run B | Run C | Run D | Run E |
| 1.00E-11 | 33 | 48 | 65 | 37 | 39 |
| 1.78E-11 | 49 | 71 | 87 | 87 | 91 |
| 3.16E-11 | 125 | 133 | 127 | n/a | 131 |
| 5.62E-11 | 178 | 213 | 237 | n/a | 238 |
| 1.00E-10 | 287 | 316 | 321 | n/a | 305 |
| Parameters | | | | | |
| Run Length | 4000 | 8000 | 8000 | 8000 | 8000 |
| K1f | 2 | 10 | 2 | 20 | 20 |
| K1r | 40 | 200 | 40 | 400 | 400 |
| K2f | 1 | 5 | 1 | 10 | 10 |
| K2r | 8000 | 40000 | 8000 | 80000 | 80000 |
| DeltaT | 1 | 5 | 1 | 1 | 1 |
| Prob=1 | $10^5$ | $10^5$ | $10^5$ | $10^6$ | $10^6$ |

# Receptor Saturation vs. Ligand Concentration



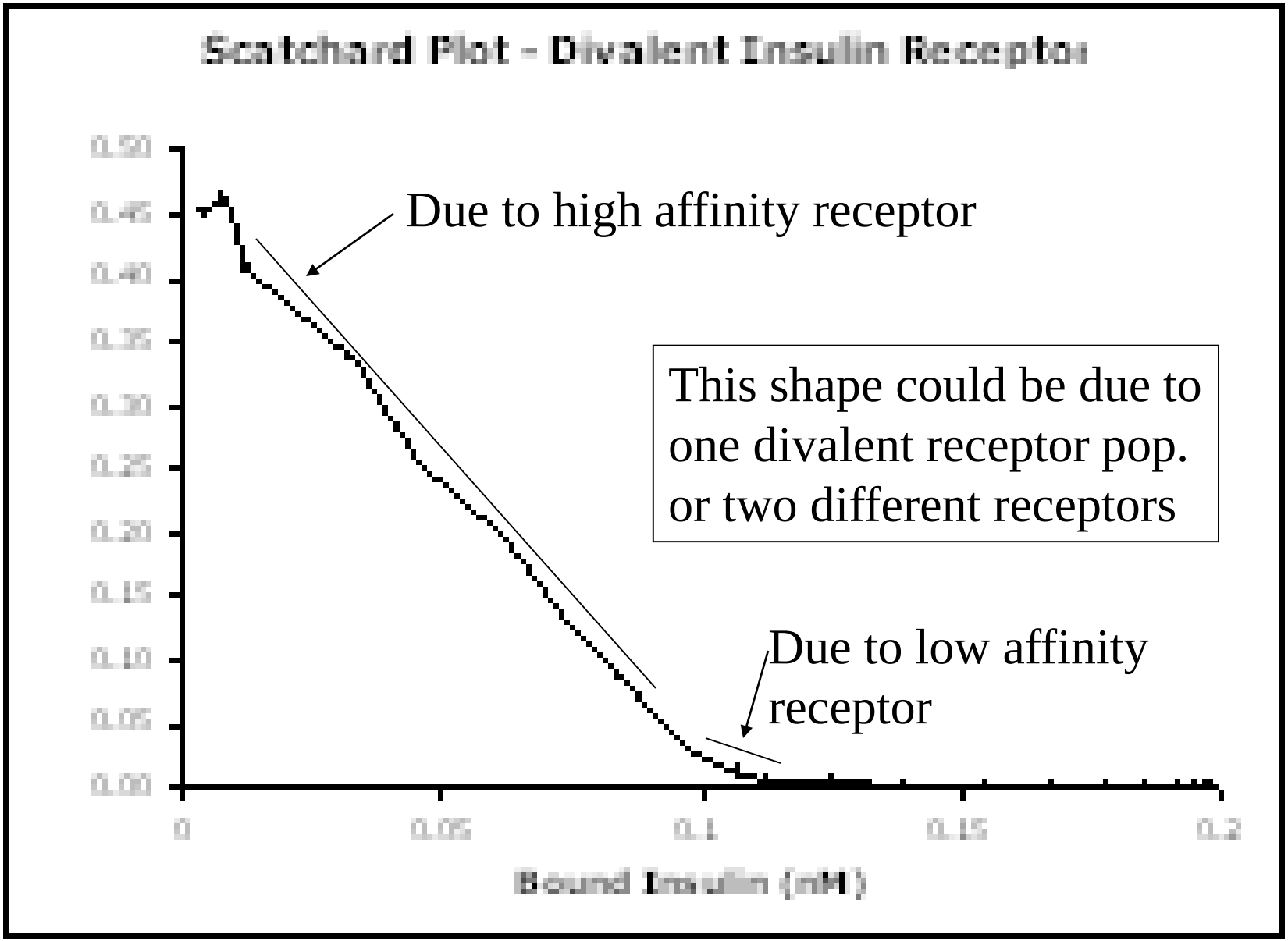

- Shows the expected rectangular hyperbola.

# Sigmoidal Log Dose-Response Curve




• The shape is more complex due to the presence of both high affinity and low affinity binding sites

# Scatchard plot, divalent insulin receptor



# Comments about ABS

- Visualization is excellent
  - Can watch the binding process (if desired)
  - Can capture the variability at low concentrations
- The “rules” are embedded in computer programs
  - Less accessible, perhaps, but not entirely
  - Likely to foster collaboration between modelers and biomedical researchers
- Starlogo has appreciable limitations
  - Requires considerable “baby-sitting” when making multiple, long runs
  - Would often simply quit running after a number of hours
    - “memory leak”?

# Overall Comparison of SD and ABS

| | System Dynamics (STELLA) | Agent Based Simulation (StarLogo) |
|---|---|---|
| **Overall approach** | • Abstract state variables and equations<br>• Equations solved to simulate behavior over time | • Physical emulation of "agents" and their "rules" for interaction |
| **Mathematics** | • Calculus<br>• Numerical integration of diff. equations | • Logic, algorithms<br>• Simple probabilities |
| **Ease of Communication** | + model structure<br>+ numerical results | + behavior/interaction of individual entities |
| **Educational potential** | + May help to demystify compartmental analysis | + Closely mimics actual physiological processes and experimental lab procedures |

# SD and ABS Comparison (cont.)

| | System Dynamics (STELLA) | Agent Based Simulation (StarLogo) |
|---|---|---|
| **Biomedical research relevance** | • Modeling aggregate behavior<br>• Does not mimic the behavior and dynamics at the entity level<br>• Cannot show when the aggregate behavior might depart from statistical means<br>• Likely to increase<br>  ○ As S/W gets more user friendly<br>  ○ As S/W evolves to better fit biomedical research needs | • Modeling movement, interaction, and state changes of individual entities<br>• Inefficient at modeling very large numbers of interacting entities<br>• Process of running experiments on the computer closely resembles the actual experimental process significantly increases relevance |