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

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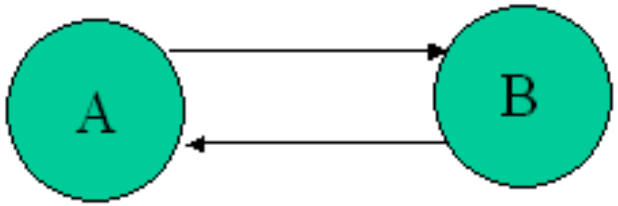
The Questions

- 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

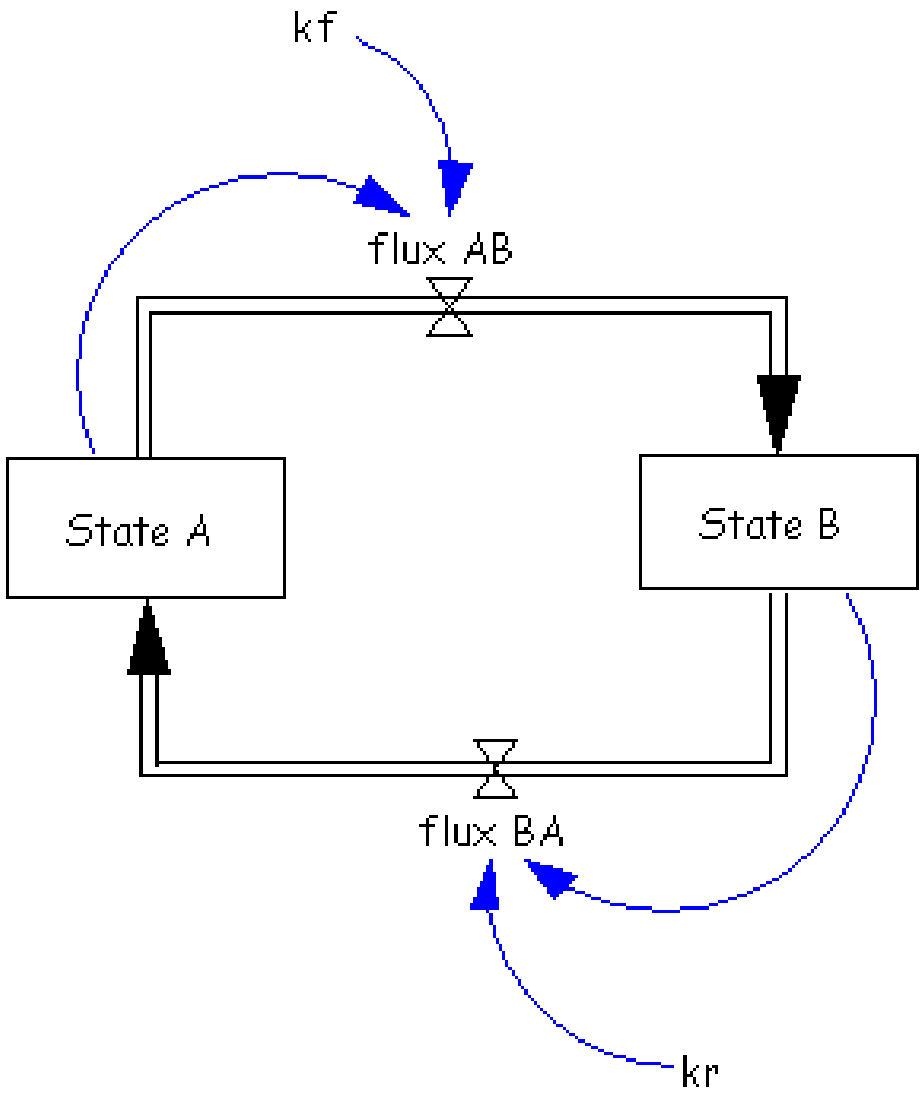
- LR_associations/time = R • k1_f_EFF
  - Assuming constant ligand concentration
  - Binding decreases as unbound receptor R is depleted.

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

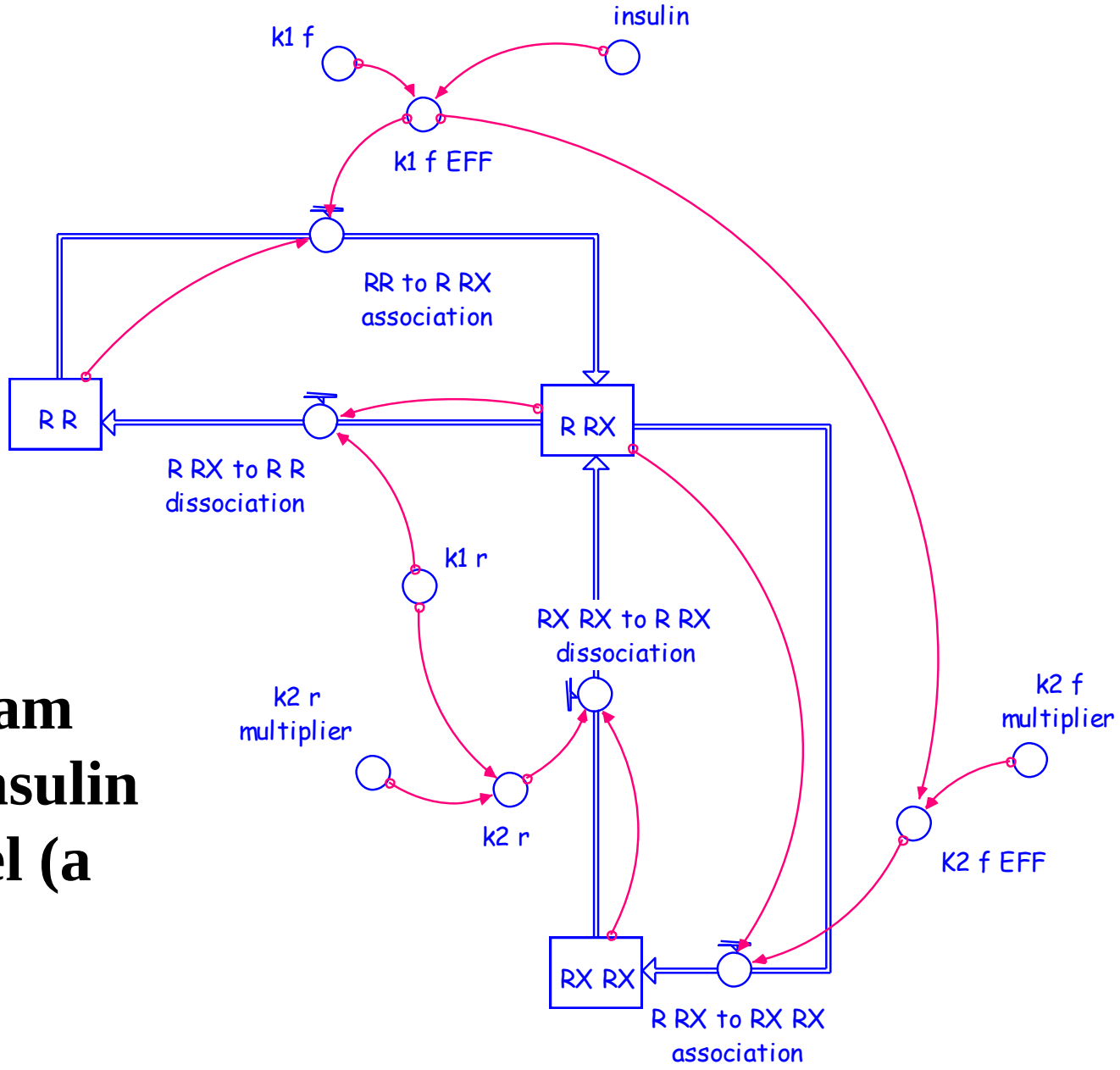
- LR_dissociations/time = LR • k1_r

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

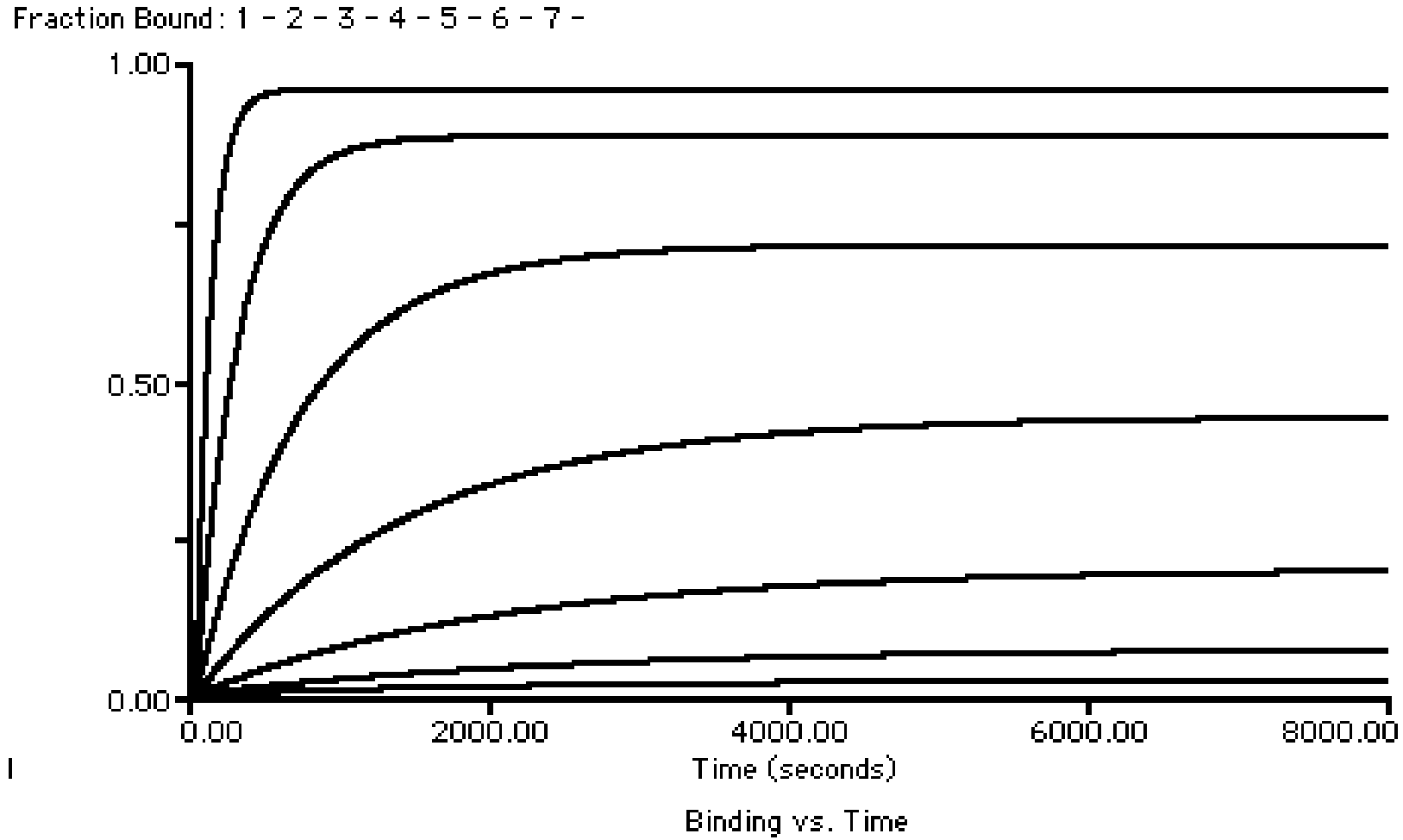
SD Flow diagram for generic 2SE model



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



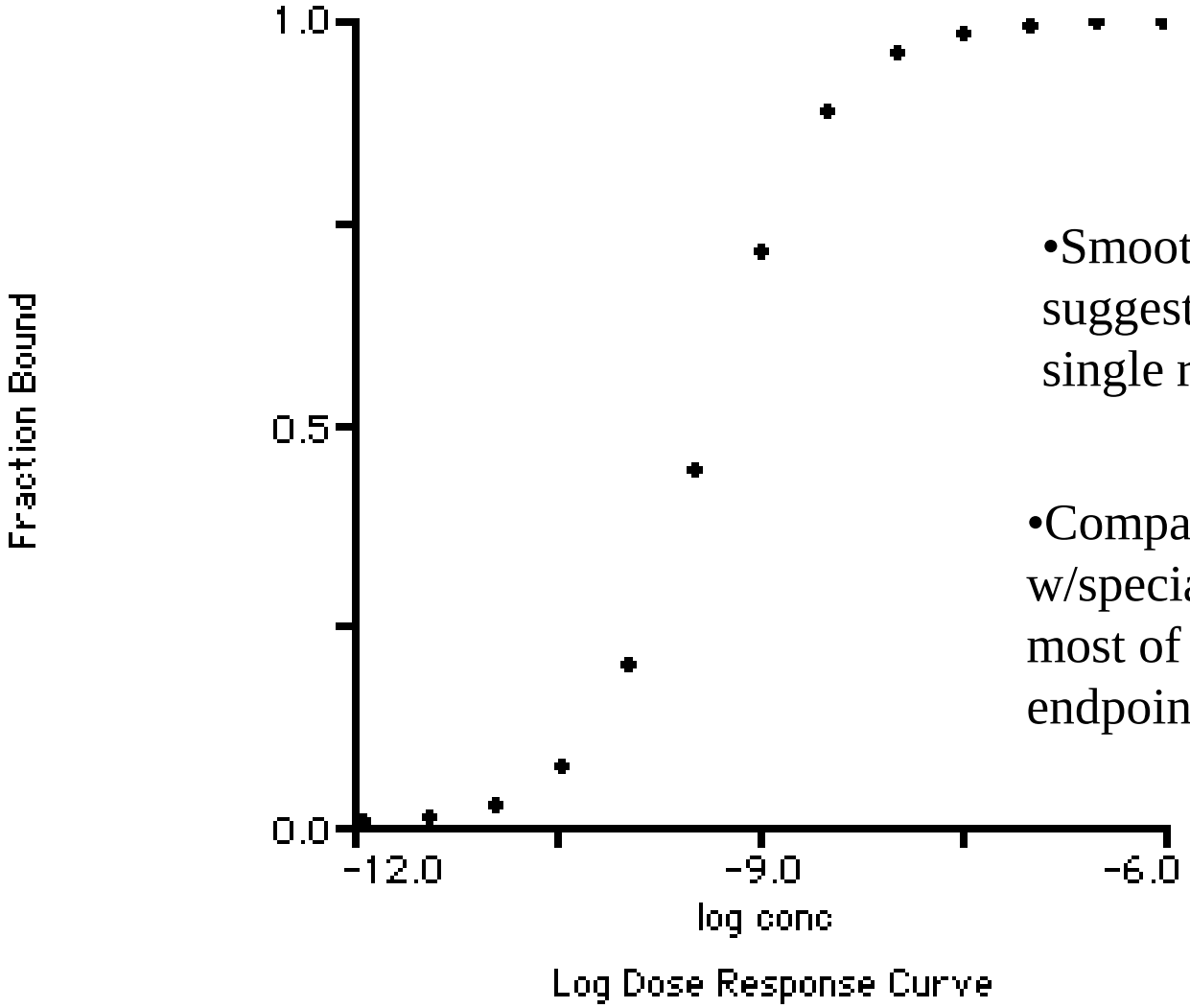
Fraction bound over time with different ligand concentrations (using sensitivity analysis feature)



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…

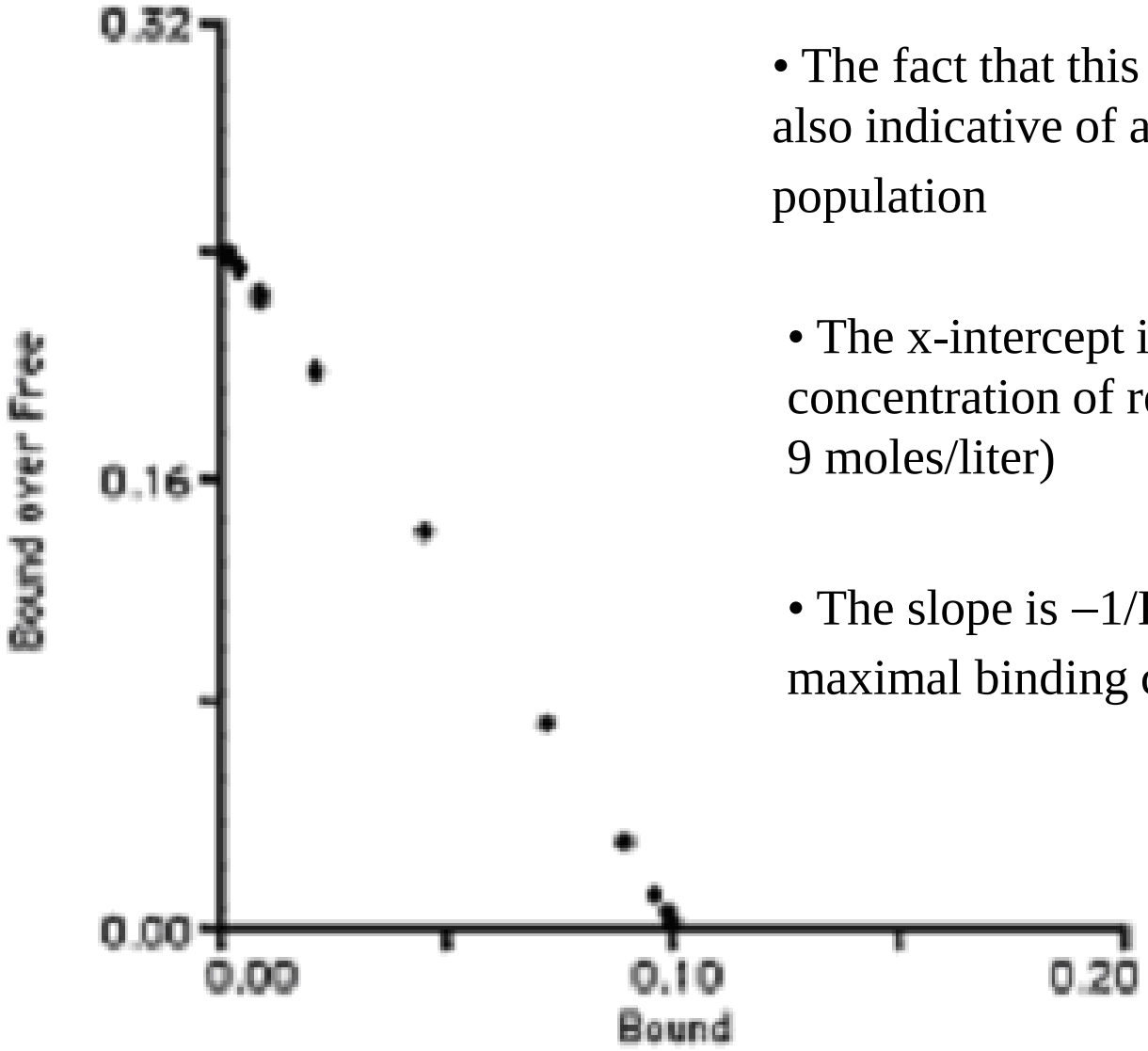
Log dose-response curve



- 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

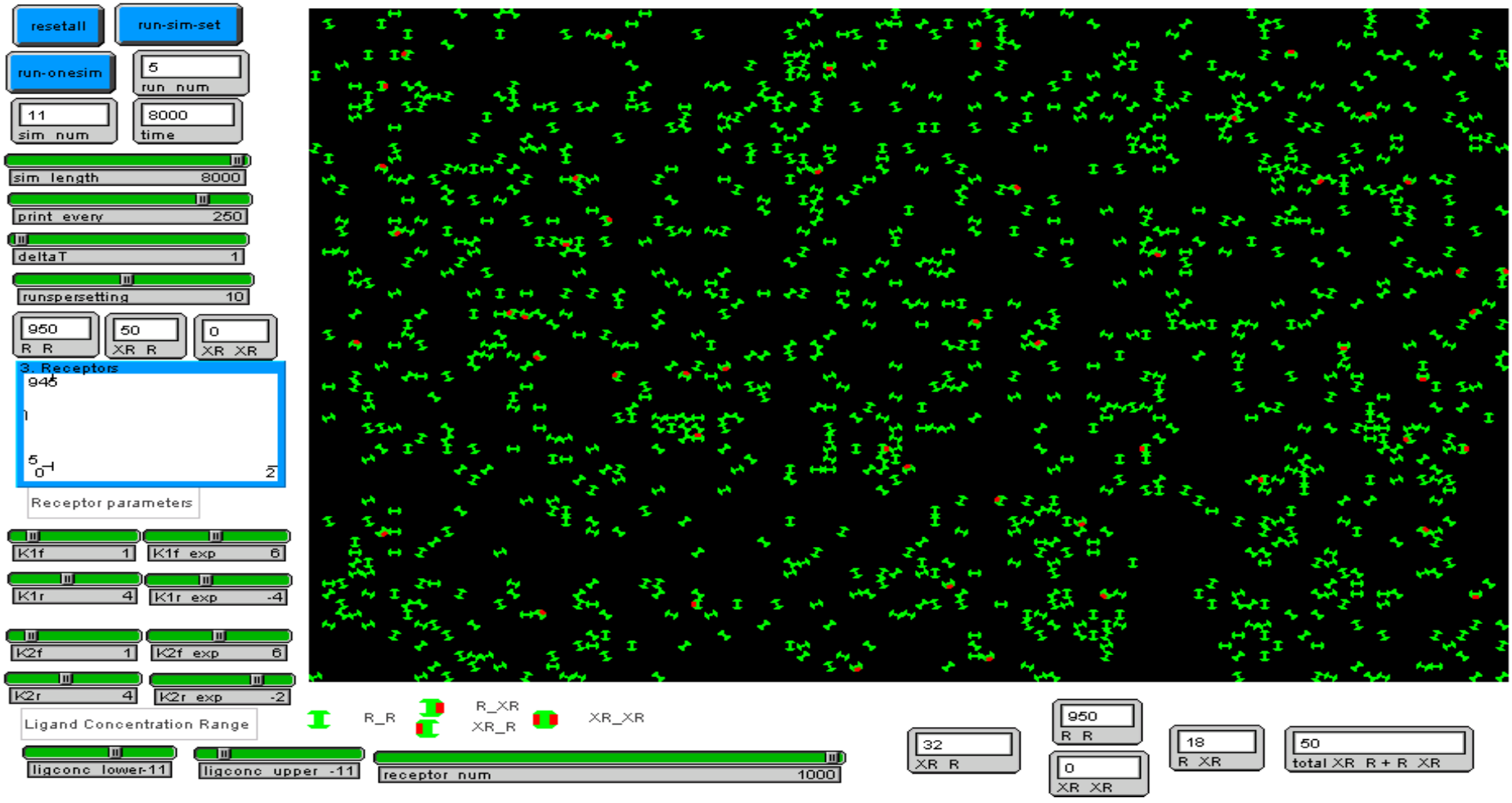
Comments about SD Modeling

- 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

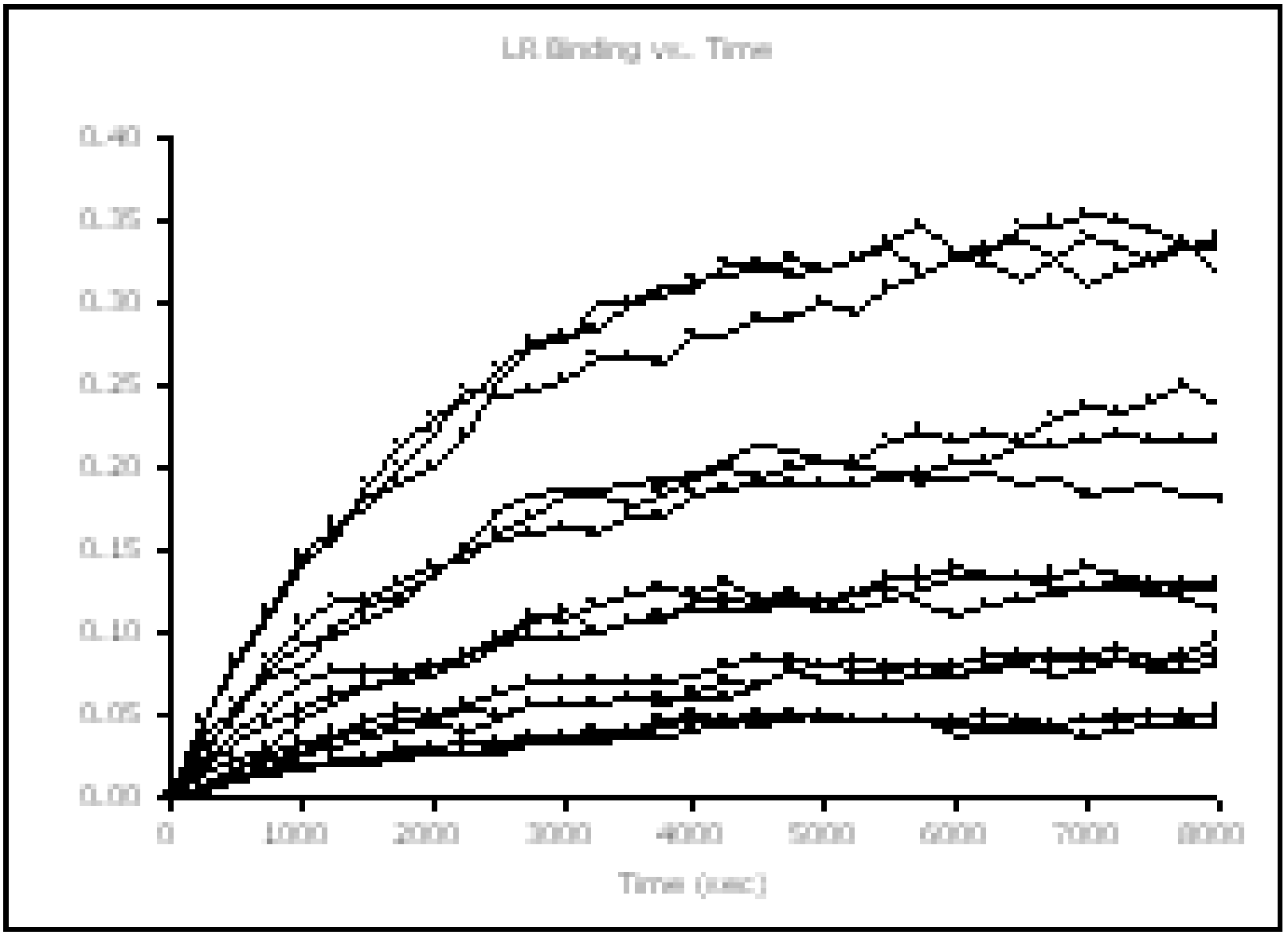
```
to calc-keffs
  setK1f_eff1000000 1000000 * 2 * ligconc
* K1f * (10 ^ K1f_exp) * deltaT
  setK2f_eff1000000 1000000 * ligconc *
K2f * (10 ^ K2f_exp) * deltaT
  setK1r1000000 1000000 * K1r * (10 ^
K1r_exp) * deltaT
  setK2r1000000 1000000 * 2 * K2r * (10 ^
K2r_exp) * deltaT
```

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

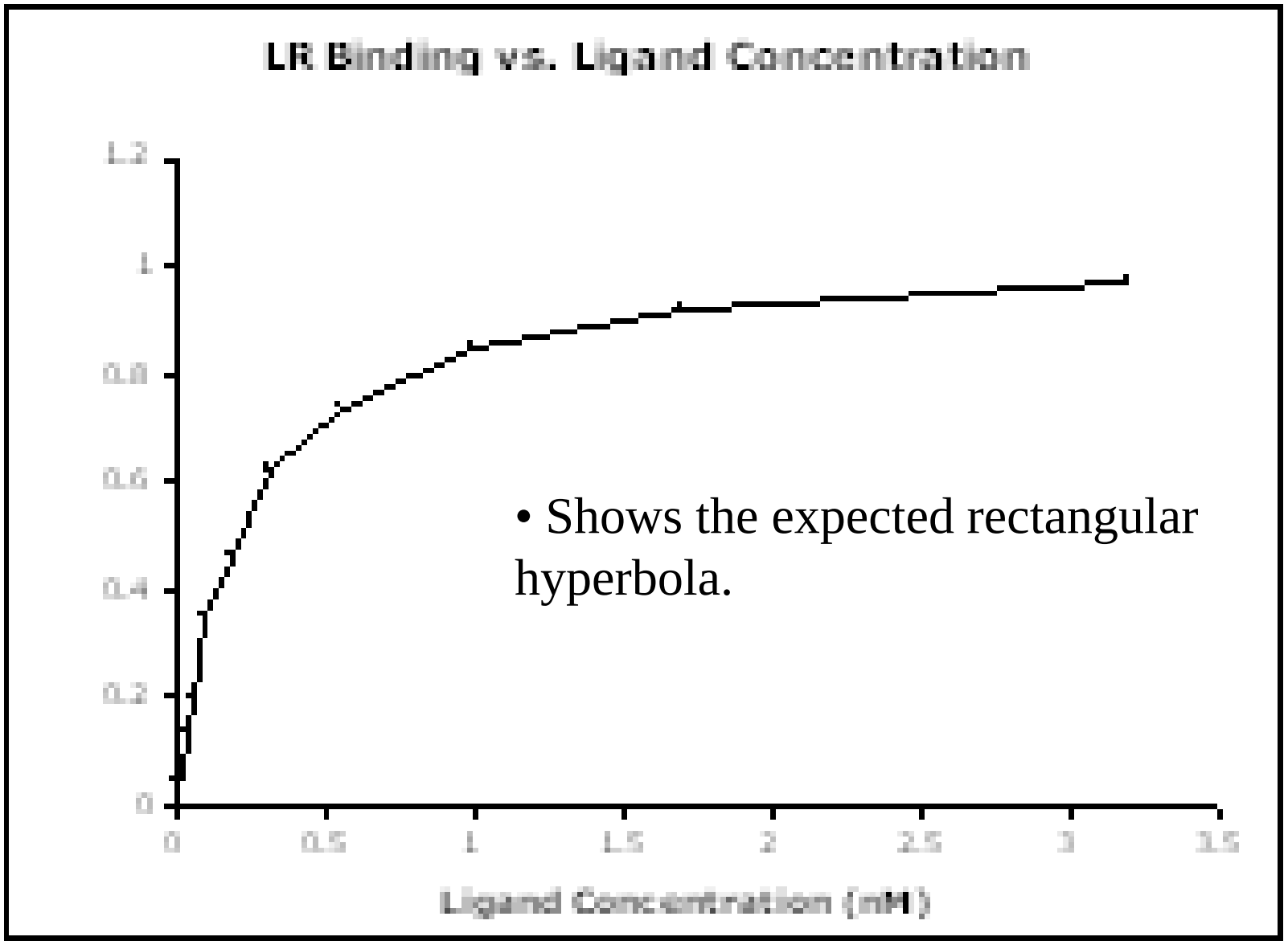
Ligand-receptor binding vs. time (N=1000, 3 runs/conc.)



Lab notes regarding multiple model runs at low concentrations

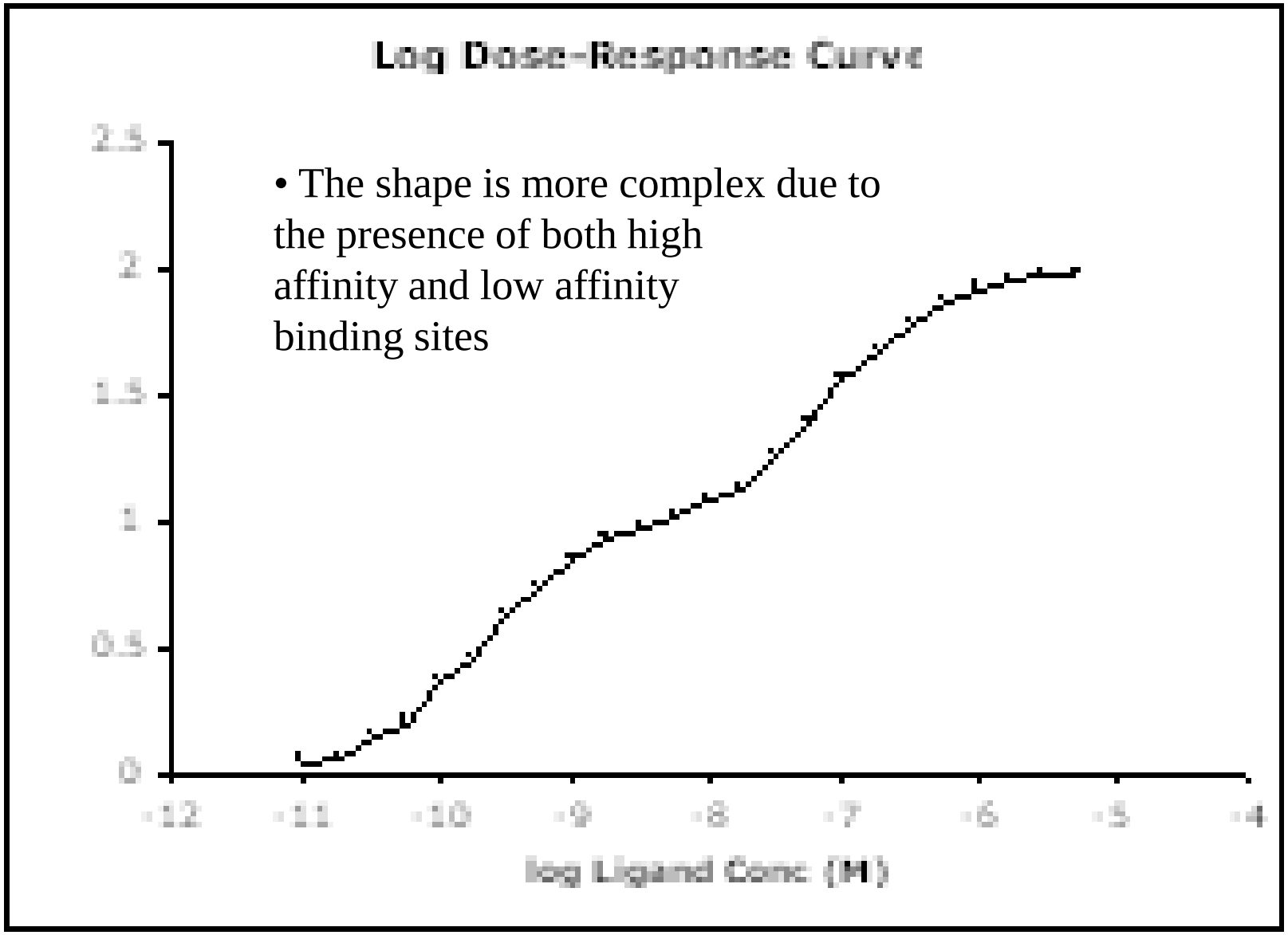
	Final # Bound				
Concen-tration	Run A	Run B	Run C	Run D	Run E
1.00E-11	33	48	65	37	39
1.78E-11	49	71	87	87	91
3.16E-11	125	133	127	n/a	131
5.62E-11	178	213	237	n/a	238
1.00E-10	287	316	321	n/a	305
Parameters					
Run Length	4000	8000	8000	8000	8000
K1f	2	10	2	20	20
K1r	40	200	40	400	400
K2f	1	5	1	10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



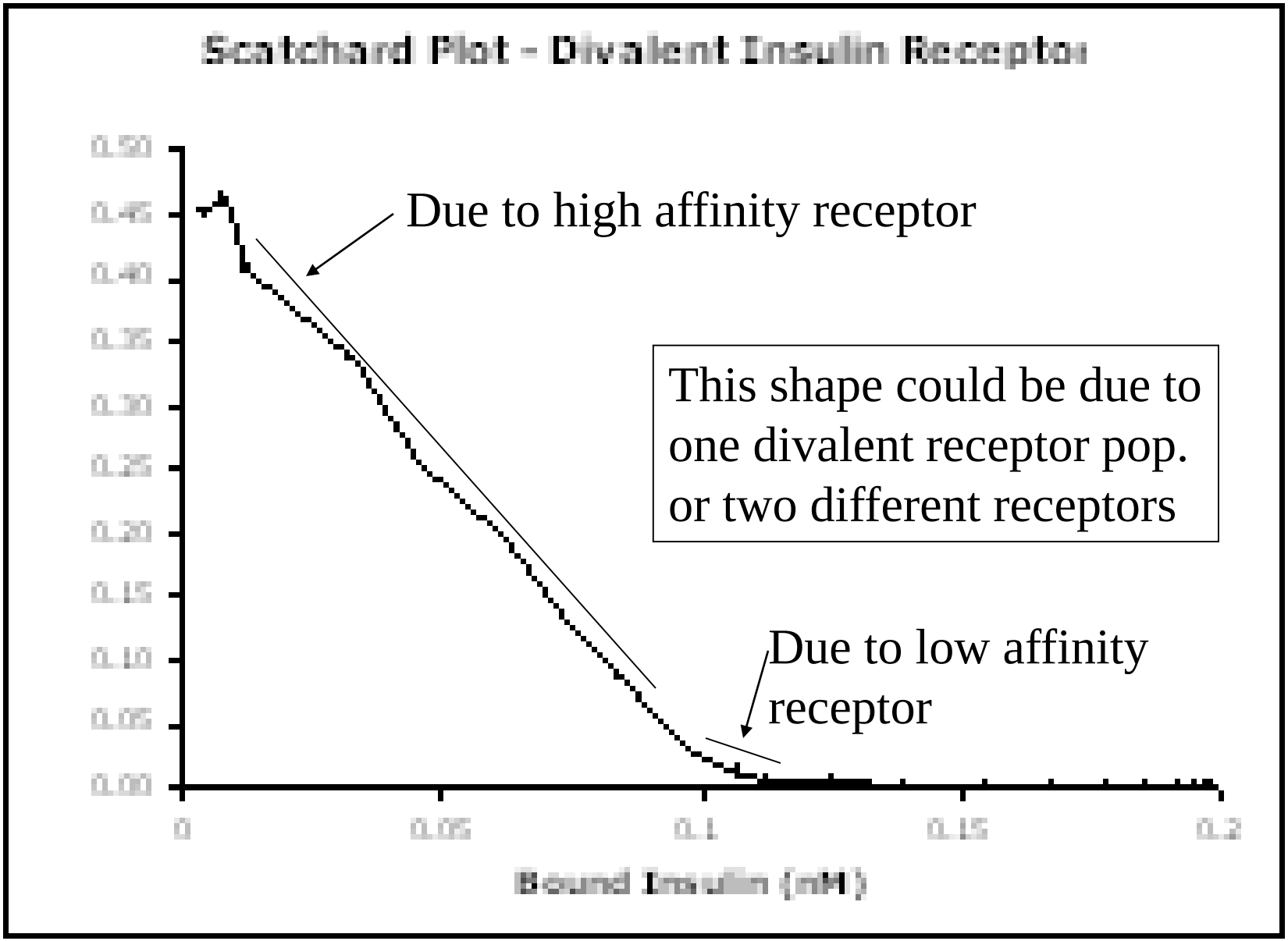
- Shows the expected rectangular hyperbola.

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 • Equations solved to simulate behavior over time	• Physical emulation of "agents" and their "rules" for interaction
Mathematics	• Calculus • Numerical integration of diff. equations	• Logic, algorithms • Simple probabilities
Ease of Communication	+ model structure + 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
	• Does not mimic the behavior and dynamics at the entity level
	• Cannot show when the aggregate behavior might depart from statistical means
	• Likely to increase
	  ○ As S/W gets more user friendly
	  ○ As S/W evolves to better fit biomedical research needs
		• Modeling movement, interaction, and state changes of individual entities
		• Inefficient at modeling very large numbers of interacting entities
		• Process of running experiments on the computer closely resembles the actual experimental process significantly increases relevance