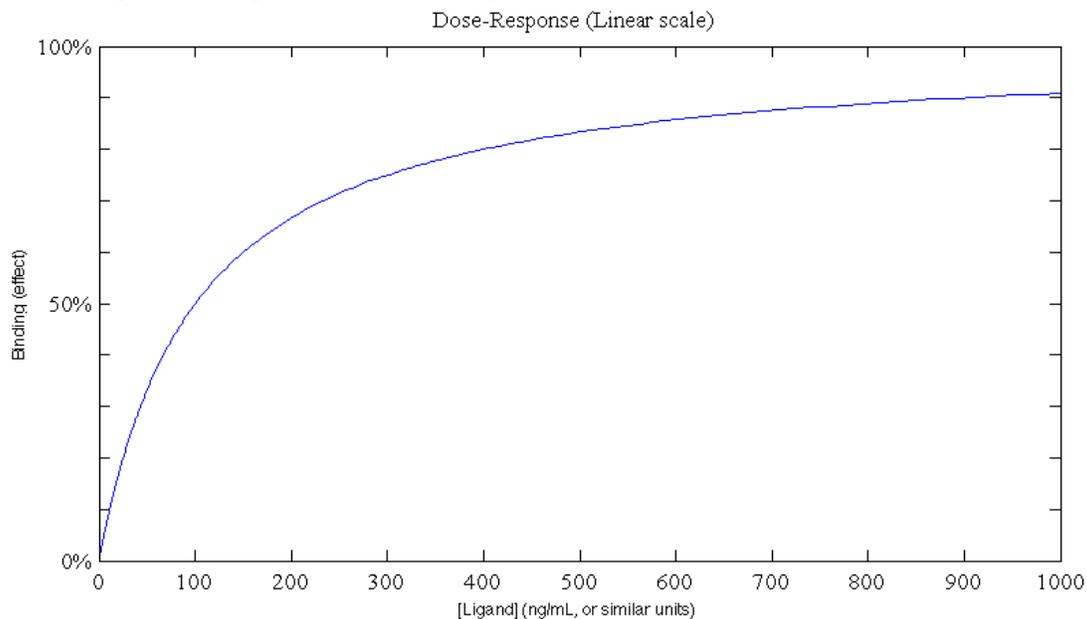


Dose-Response Curves and Intrinsic Efficacy
by Zak Fallows
2009-12-14

Many real-life dose-response curves are complex or poorly understood. However, some are well understood and follow simple models.

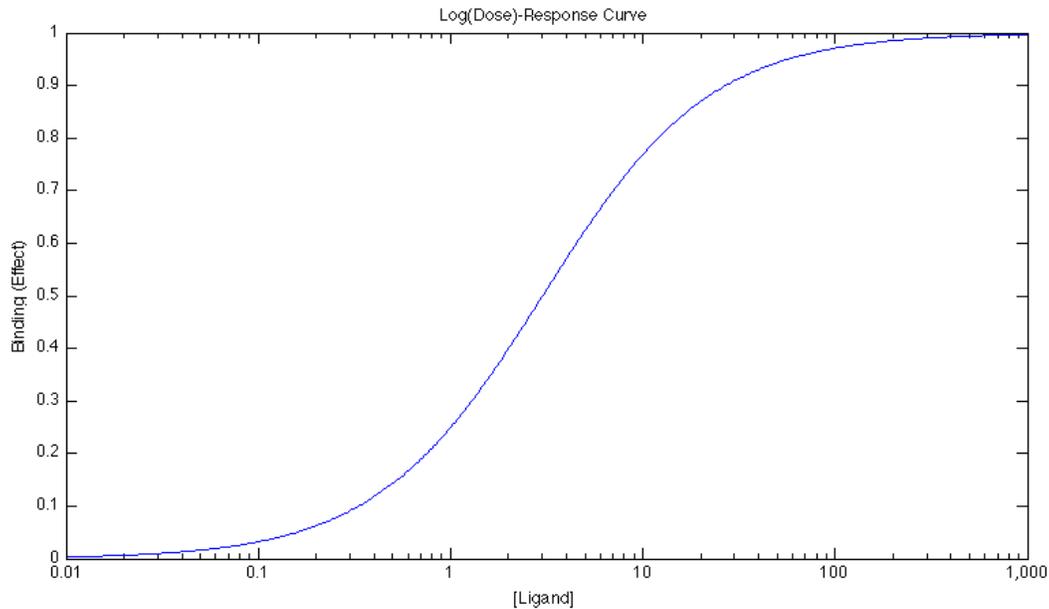
The **Michaelis-Menten** model is quite simple and very accurate in some situations. This model is often used to describe enzymatic reactions where a substrate molecule binds to an enzyme, but it can also be used to describe a ligand binding to a receptor. In both cases, the amount of binding is proportional to the [ligand] (the concentration of ligand) when [ligand] is low, and the amount of binding asymptotically approaches a maximum when [ligand] is high and the enzyme/receptor is **saturated**.

For some receptor and ligand, the curve might look like this:



The above curve is a hyperbola, with the same shape as $1/x$, but it is flipped and shifted up and left, and scaled.

Now, if we plot the binding of a different ligand (with higher affinity) for its receptor, but use a **logarithmic x-axis scale**, we get something like this:



The above graph has the same shape as the **logistic curve**, simply because we are using a logarithmic scale.

- Notice that this semi-log curve approaches y-min asymptotically to the left, and y-max asymptotically to the right
- Notice that the curve looks exponential near y-min and y-max
- Notice that the curve is just a line at the inflexion point, $x = \log(\text{EC}_{50})$, $y = (\text{max} - \text{min})/2$

Please email me, pharmacology@mit.edu, if you would like to talk about the underlying math and see some derivations.

Now, let's examine the concepts behind Exam 2, Question 8 while keeping all this in mind.

Competitive and noncompetitive inhibition

The NMDA receptor in reality has very complex kinetics, and NMDA receptors are constructed from a combination of subunits so there are a huge number of possible permutations, each with different kinetic parameters. However, let us oversimplify the NMDA receptor to say that it has just one glutamate binding site with simple first-order kinetics (Michaelis-Menten kinetics).

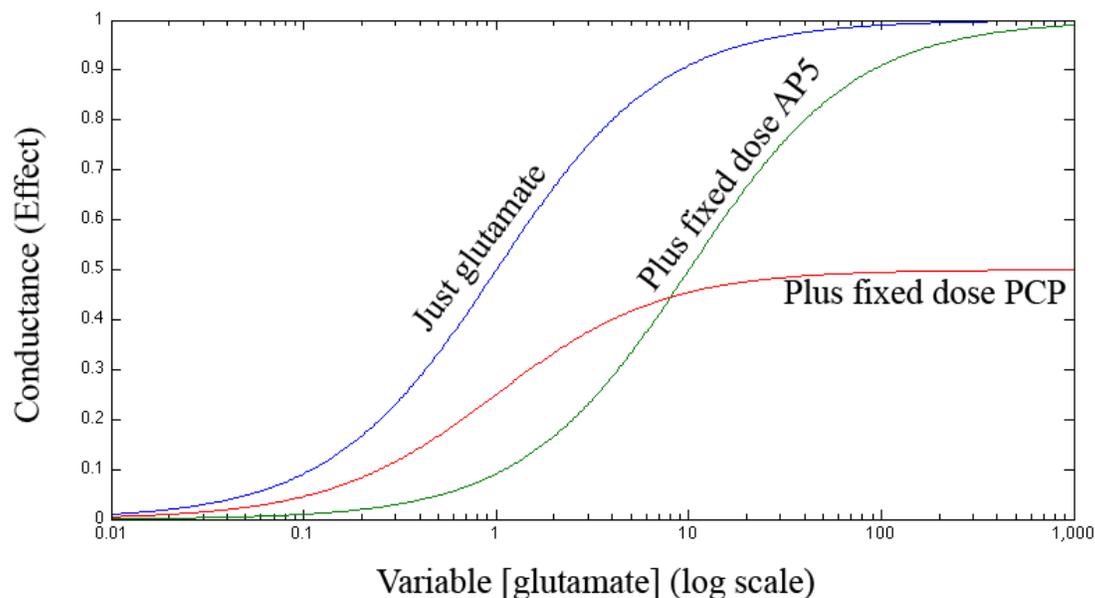
Draw a log(dose)-response curve for the NMDA receptor, with the y-axis of conductance (effect), and the x-axis of log([glutamate]). Assume some fixed concentration of Mg^{++} , and some fixed concentration of glycine or D-serine, and some fixed membrane potential. Phew, see how many assumptions we have to make to make the curve look a predictable shape? Don't worry, the difference between competitive and noncompetitive antagonism is really important

clinically and theoretically. The only problem is that the real life graphs are not so pretty sometimes.

Draw the curve with just variable [glutamate].

Now add a fixed dose of PCP, and draw the curve for variable [glutamate]. (This is a classical **noncompetitive antagonist**, so it just squishes the curve down. It may also be an uncompetitive antagonist, but don't worry about what that means. That feature doesn't even matter in our case, because we stipulated fixed and arbitrary membrane potential.)

Now add a fixed dose of AP5, and draw the curve. (This is a classical **competitive antagonist** at the glutamate binding site. It shifts the curve right.)



Note that all units are arbitrary.

Intrinsic Efficacy

Sadly, we cannot use the NMDA receptor as an example for intrinsic efficacy (IE). The most common textbook example would be the μ (μ) opioid receptor, which has full agonists (morphine), partial agonists (buprenorphine), and antagonists (naloxone), all of which are used clinically. The clinical effects of these drugs corresponds perfectly with their intrinsic efficacy:

- Morphine, a full μ agonist, causes death in overdose (by depressing respiration).
- Buprenorphine (Suboxone®), a partial μ agonist, is generally nonfatal in overdose (and also less euphoric).
- Naloxone (Narcan®), a competitive μ antagonist, can be administered to patients who are overdosing on opioids because it reverses the overdose and often causes immediate withdrawal symptoms.

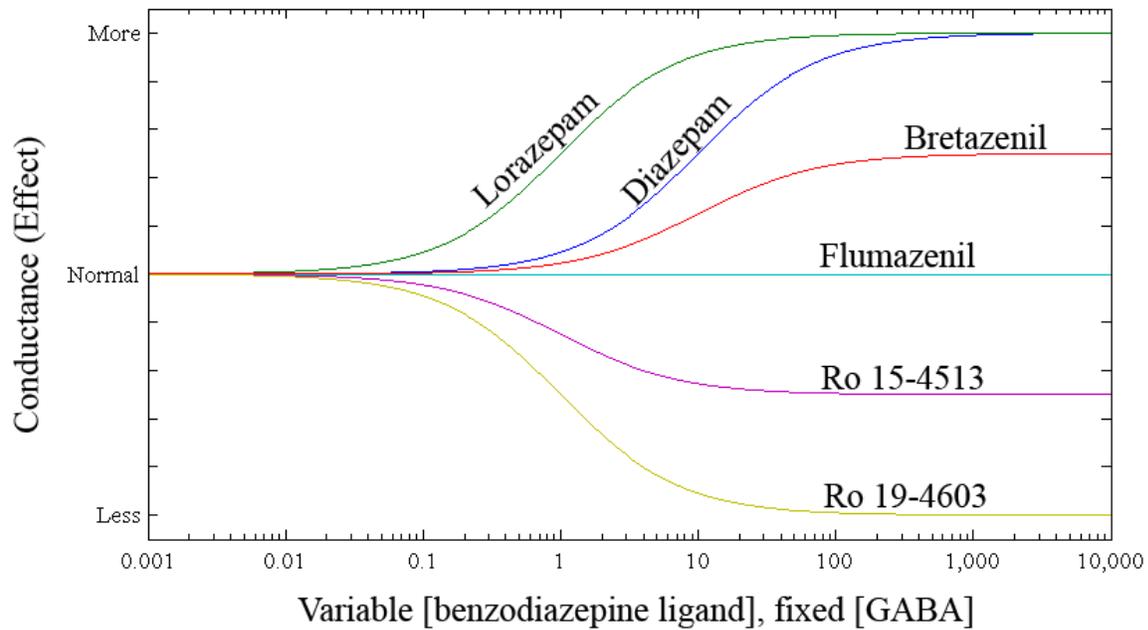
A textbook example for inverse agonists would be the histamine receptor, because Benadryl, Zyrtec, Claritin, and Unisom are all inverse agonists. However, let's consider the benzodiazepine receptor.

The “benzodiazepine receptor” is just a particular binding site on the GABA_A receptor, but we could rename it the “benzodiazepine receptor” if we just changed our point of view a bit. We would then say that the benzodiazepine receptor is noncompetitively modulated by GABA, and GABA is a requisite coagonist for the benzodiazepine receptor, just like glycine is a requisite coagonist at the NMDA receptor. In fact, there are some GABA_A receptors in the brain that do not even require GABA, such as the $\alpha_6\beta\gamma$ receptor. The $\alpha_6\beta\gamma$ GABA_A receptor is constitutively open regardless of the concentration of GABA, but can be closed by certain other ligands (e.g. Ro 15-4513).

Consider a benzodiazepine receptor with a fixed concentration of [GABA]. Now, draw a graph with the y-axis “conductance” or “effect” and the x-axis $\log([\text{benzodiazepine site ligand}])$. Notice that the concentration of GABA is **fixed**, because we are treating GABA as a coagonist. The concentration of the benzodiazepine ligand is what varies along the x-axis.

- i. Draw the curve with benzodiazepine site ligand = None. Is conductance zero? No, because there was some fixed amount of [GABA]. So the graph is a nice flat line at some positive value.
- ii. Draw the curve with BZD ligand = diazepam, a full agonist. Now, note that $\log([\text{diazepam}])$ is the x-axis, NOT $\log([\text{GABA}])$. We chose some fixed amount of GABA.
- iii. Draw the curve with BZD ligand = bretazenil, a partial agonist that is in clinical trials as an anxiolytic with lower abuse potential and withdrawal than full agonists like diazepam.
- iv. Draw the curve with BZD ligand = flumazenil, an antagonist. (this is a flat line, same level as “None”)
- v. Draw the curve with BZD ligand = diazepam, plus a FIXED dose of flumazenil. (shifted right relative to diazepam alone)
- vi. Draw the curve with BZD ligand = Ro15-4513, a partial inverse agonist. JUST KIDDING, you don't know how far down the minimum should go. What does “partial” mean? Relative to what? Can a full BZD inverse agonist block off the ion channel completely, or can it only bring down the conductance 50% if there is a shit-ton of GABA around?
- vii. Draw the curve with BZD ligand = Ro19-4603, the most efficacious inverse agonist known to date (the ligand with the most negative IE). The conductance should max out somewhere below normal and above 0, but you can choose the exact place arbitrarily. Heck, maybe that is the right shape for the curve at a certain concentration of [GABA] and given a certain subtype composition.

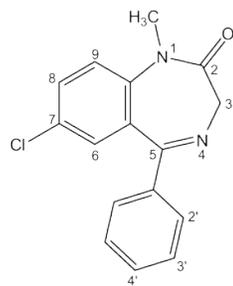
viii. Let's define the IE of Ro19-4603 to be -1, and let us say it is a full inverse agonist. This is arbitrary, but a logical choice. NOW you can do part (vi) above, draw the curve of Ro15-4513, which is a partial inverse agonist GIVEN our new definition of what "full" means.



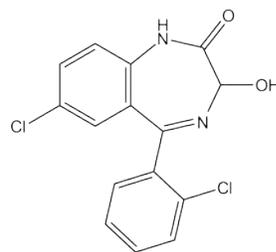
The above figure shows a full agonist, intrinsic efficacy (IE) +1 (diazepam), it also shows a **more potent** full agonist (lorazepam), an antagonist (flumazenil, IE = 0), a partial agonist (bretazenil), a partial inverse agonist, and a full inverse agonist (IE = -1).

Here are some molecular structures:

The full agonists:



Diazepam



Lorazepam

continued...
More structures:

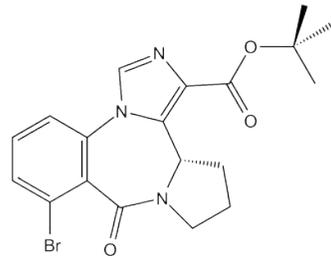


Figure 5: Bretazenil,
a partial agonist

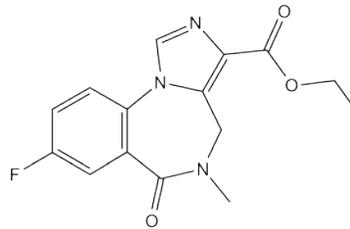


Figure 6: Flumazenil,
an antagonist

The inverse agonists:

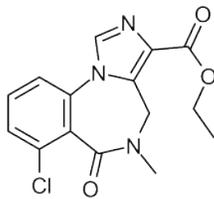


Figure 7: Sarmazenil,
Ro 15-3505

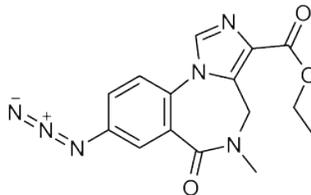


Figure 8: Ro 15-4513

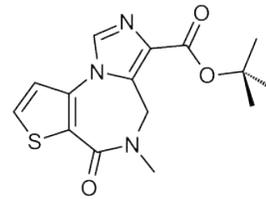


Figure 9: Ro 19-4603



The GABA_A receptor has at least five distinct and well characterized binding sites:

- GABA
- Benzodiazepine
- Barbiturate
- Picrotoxin
- Neurosteroid (the IV general anesthetic alphaxolone works via this site, how hilariously awesome is that? It's a steroid that puts you out for surgery!)

The GABA_A receptor also binds several other ligands, but it is not so clear where these bind:

- Ethanol
- EBOB
- Thujone

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