Nauta JJ, Beyer WE, Osterhaus AD. *On the relationship between mean antibody level, seroprotection and clinical protection from influenza.*

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IDIG 2022-10-25

Slides: https://wzbillings.com/presentations/IDIG-2022-10-25/

(this is a stock image that I got from powerpoint and Powerpoint said I am allowed to use it)

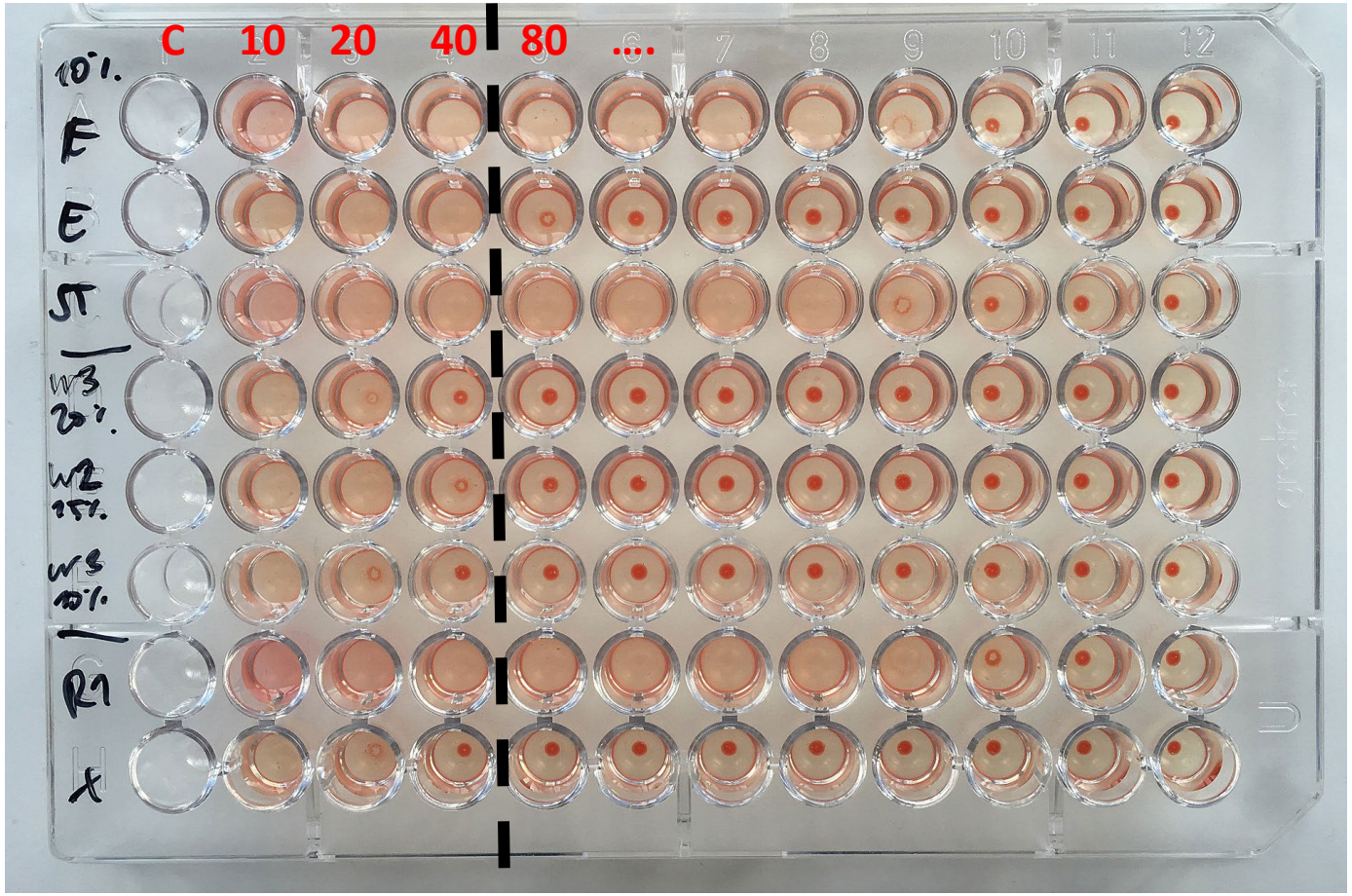
Citation

- Nauta JJ, Beyer WE, Osterhaus AD. On the relationship between mean antibody level, seroprotection and clinical protection from influenza. Biologicals. 2009;37(4):216-221. doi:10.1016/j.biologicals.2009.02.002.

Definitions (general)

- **CoP** (correlate of protection): an immunological measurement that is statistically associated with clinical protection from a condition.
- **Seroprotection**: having a serological measurement higher than some predetermined titer (usually the titer determined to be associated with 50% clinical protection).
- **Seroconversion**: an individual's serological measurement is lower than the threshold before an intervention, but is above the threshold after the intervention. (Protection + the intervention did it.)
- **Clinical protection**: reduced risk for an individual to acquire a condition.

HAI and the magical 1:40 titer



https://commons.wikimedia.org/wiki/File:Hemagglutination_assay.jpg

Background/motivation

- HAI is a CoP for flu
- We can therefore use it to measure vaccine efficacy
- How do mean HAI titer, seroprotection, and clinical protection relate? All of these are commonly used.
- **Main question:** does a higher mean titer or seroprotection risk always reflect an increase in clinical protection?

The model

$$t = \log_2 (\text{HAI titer}/5)$$

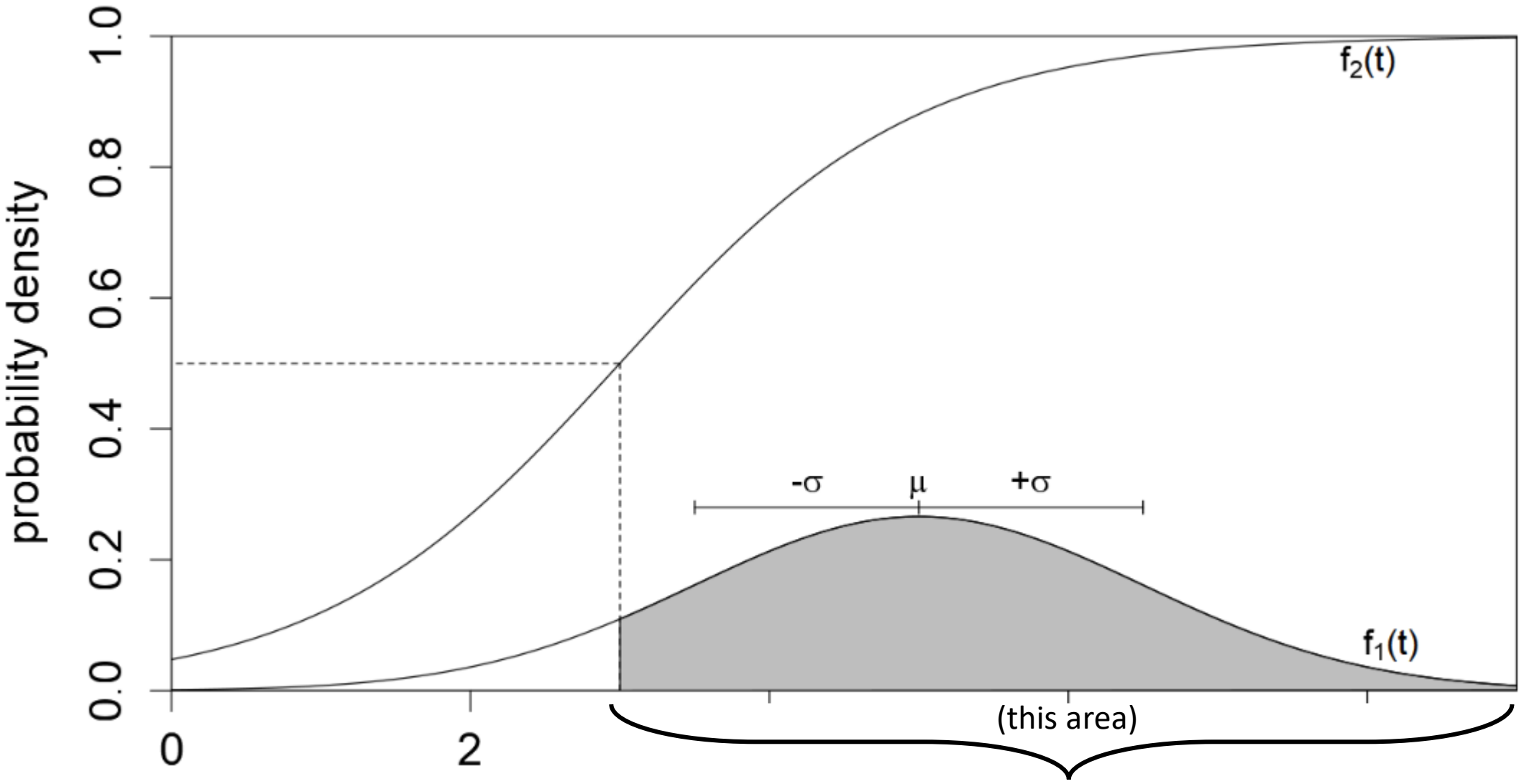
$$t \sim \text{Normal}(\mu, \sigma)$$

$$\pi_{\text{seroprotection}} = \int_{t_p}^{\infty} f(t)\ \mathrm{d}t$$

$$\pi_{\text{clinical protection}} = \int_{-\infty}^{\infty} f(t) \frac{\lambda}{(1 + \exp(\alpha + \beta t))}\ \mathrm{d}t$$

$$0 < \lambda \leq 1,\ \alpha > 0, \beta < 0$$

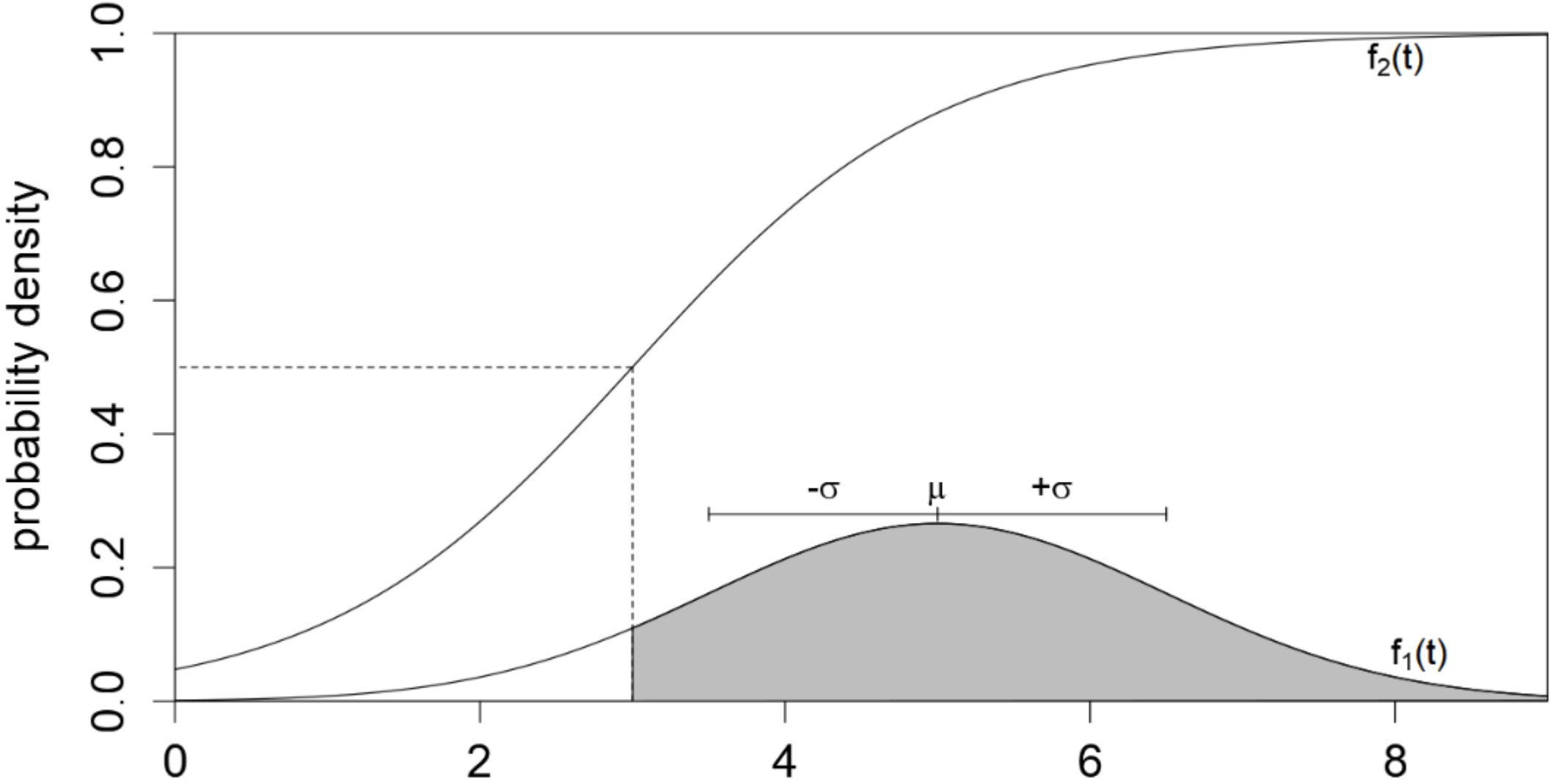
- λ is the probability of clinical protection for subjects with "a very high HI titer".
- α accounts for protection unrelated to antibody level.
- β is the slope of the clinical protection curve.



P(seroprotected) is just the calculated probability from the normal model.

$$P(t \geq 3) = \int_3^{\infty} f_1(t)\, \mathrm{d}t$$

P(clinical protection) is defined (by the authors) as the expected value of f_2.
Essentially asking the question, “What is the average value of P(clinical protection) in our model?”



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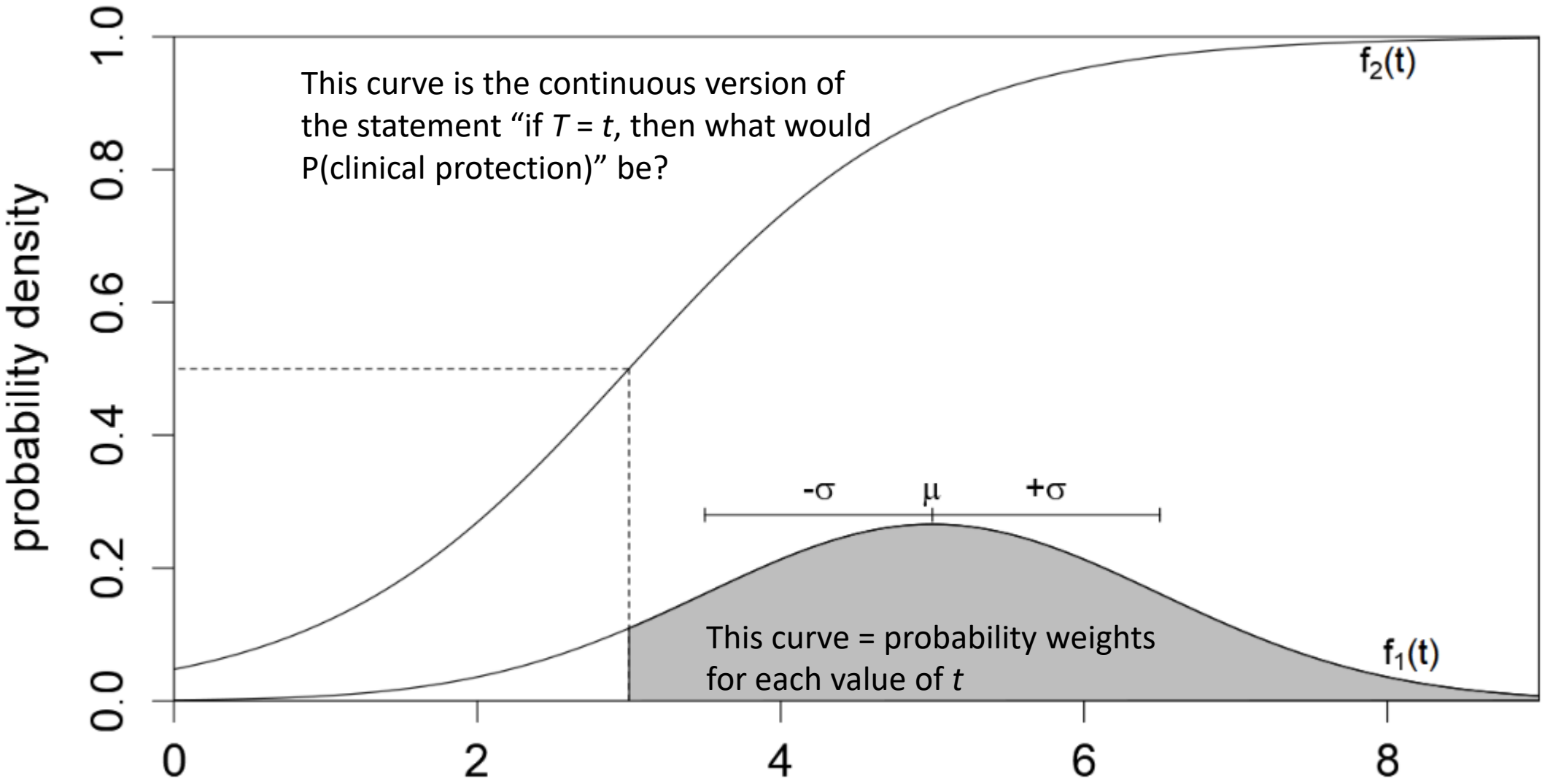
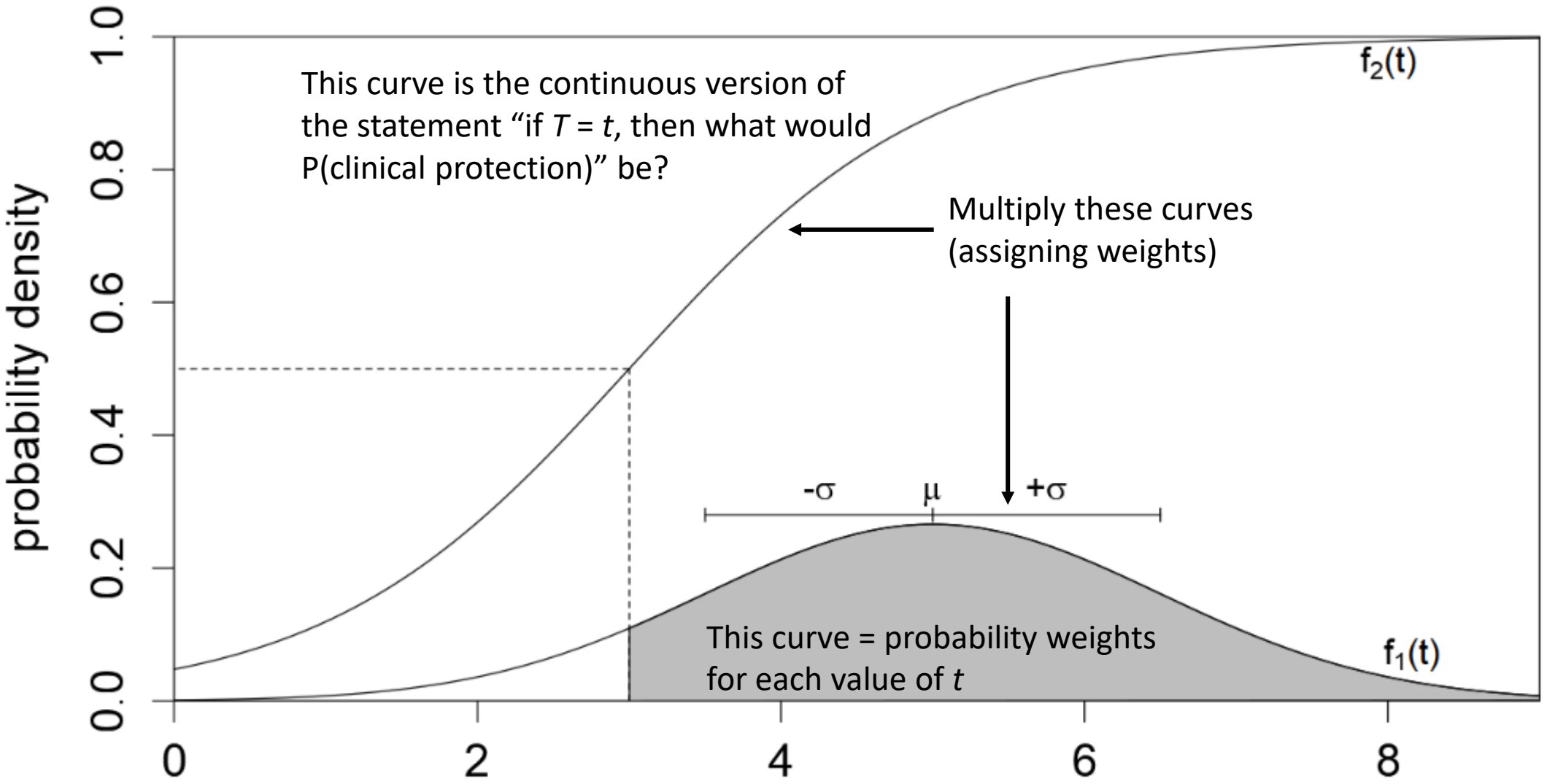
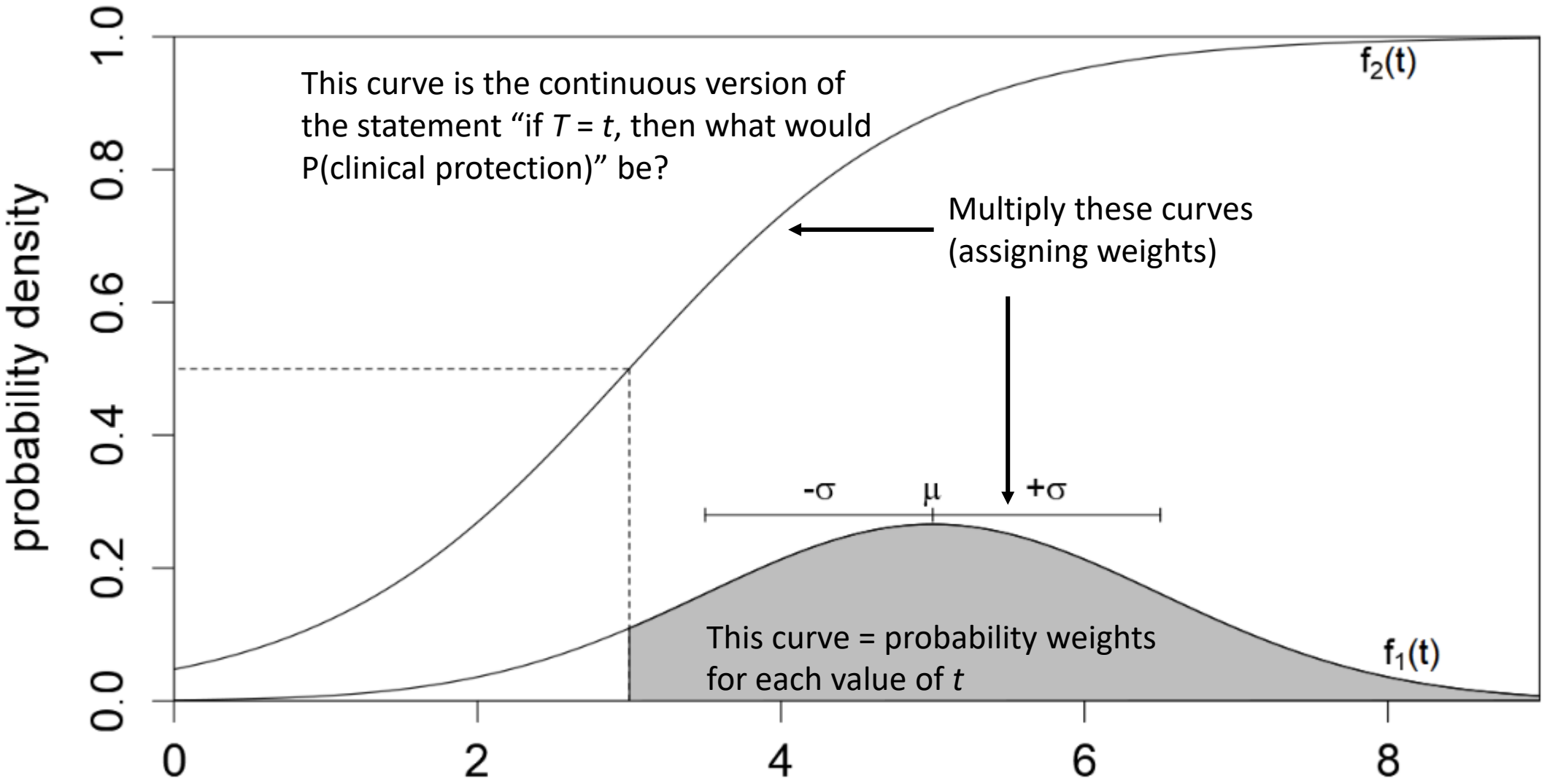


P(seroconverted) is defined (by the authors) as the expected value of f_2



P(seroconverted) is defined (by the authors) as the expected value of f_2



Then integrate (continuous version of a weighted sum)! So, P(protected) = $\mathrm{E}[f_2(t)] = \int_{-\infty}^{\infty} f_1(t)\, f_2(t)\, \mathrm{d}t$

Other thoughts about the model

- If all t were equally likely, we could just use the sample mean of $f_2(t)$.
- If one is willing to specify t_p, α, λ, then we get

$$\beta = \frac{\log(2\lambda - 1) - \alpha}{t_p}.$$

- Getting the variance/CI of this proportion? It is a hard problem. Since f_2 is monotonically increasing, for $U = f_2(T)$,

$$f_Z(z) = f_1(f_2^{-1}(z)) \left(\frac{\mathrm{d}}{\mathrm{dz}} f_2^{-1}(z)\right).$$

- Of course, one then has to identify if this is a known distribution.

anyways.

Results

- For the record, Table 3 is pretty much useless to me. As Richard McElreath says, “you can stare at a table, and it will stare back.”
- Figure 2:
  - Higher alpha = steeper slope?

  (We aren’t holding beta constant)
  - Lambda is a threshold for the max “allowed” protection probability.
  - They don’t identify which curve has which t_p. (rolling eyes emoji)

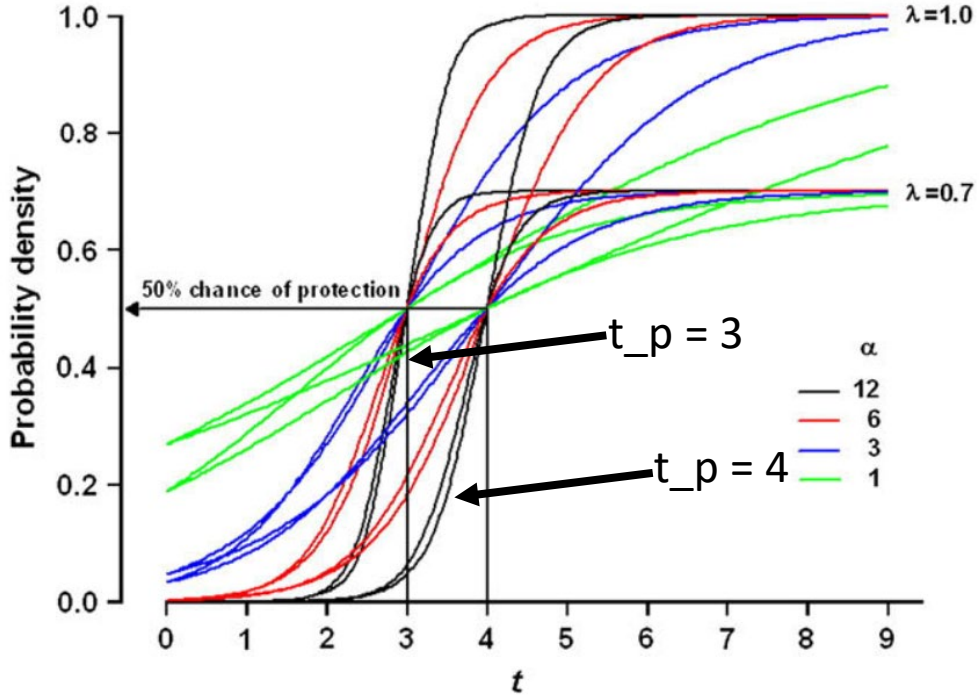


Fig. 2. Clinical protection curves examined in the statistical model.

Results

- It really bugs me when published papers have incorrectly labeled graphs.
- But the important result here is that the risk of seroprotection varies with **both** the mean and variance of *t*.
- For clinical protection, the variance is more influential the larger alpha is (no plot, stare at the table until you realize this).

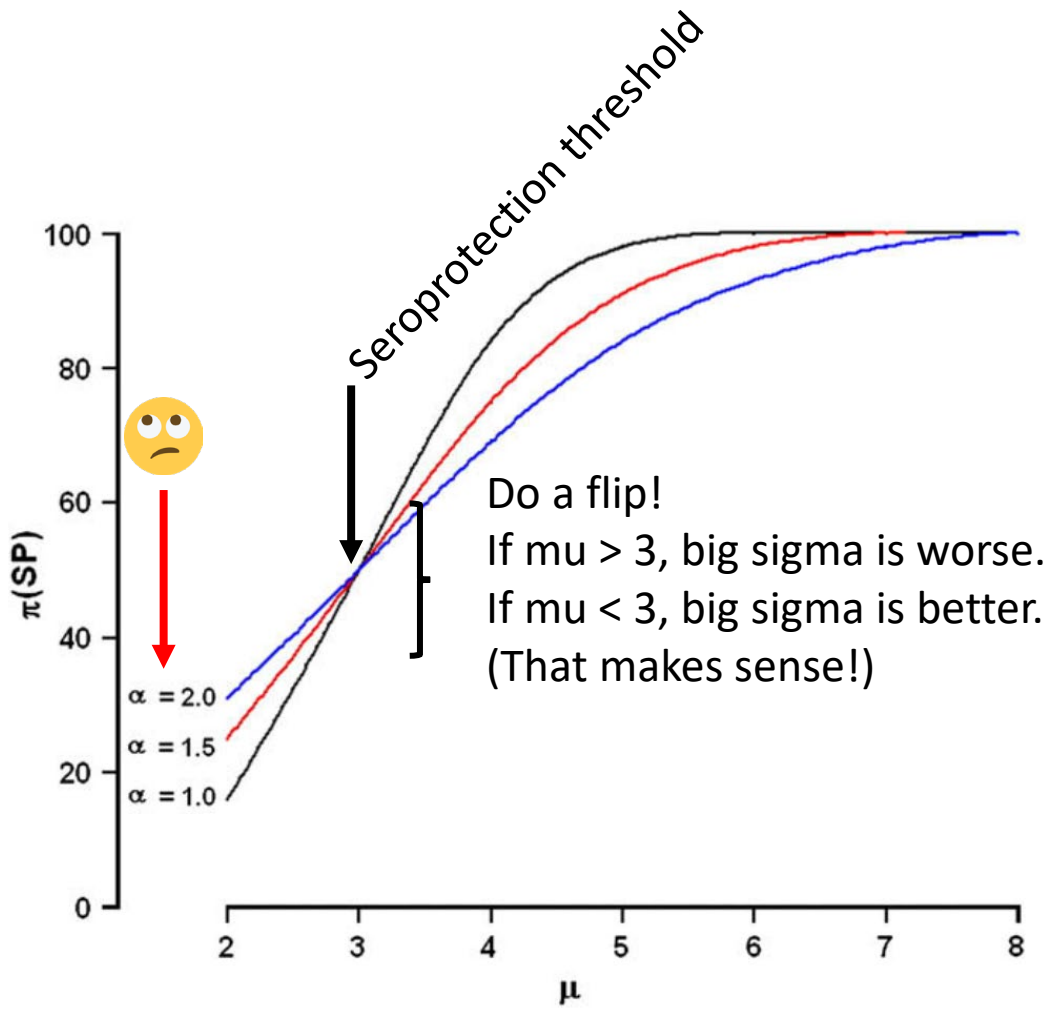


Fig. 3. Relationship between output parameter π(SP) and input parameters μ and σ.

So what?

- This makes a difference in interpreting mean titer values between two groups during a trial. The rules they provide are pretty interesting to read through. I've never seen anyone use them though.
- **Main conclusion: it is misleading to interpret differences in mean titer, seroprotection, or clinical protection without considering both the mean and variance of the titers.**

So what part 2: the mystery of the magical 1:40 titer continues

- Secondary conclusion: clinical protection levels depend on parameters for which they provide no data-based estimates. Maybe this has already been done, I haven't checked. If not, flu surveillance datasets do exist and this could be interesting.
- It would also be easy to do a much more in-depth simulation/modeling study than they did here.
- HOWEVER, their conclusions are explicitly based on the $t = 3$ (i.e. magical 1:40) threshold. Where does it come from, is it strain-specific, and is it even valid?