Strain panel design

Strains needed to compare the breadth, magnitude, and distances in human and ferret sera

Overall logic

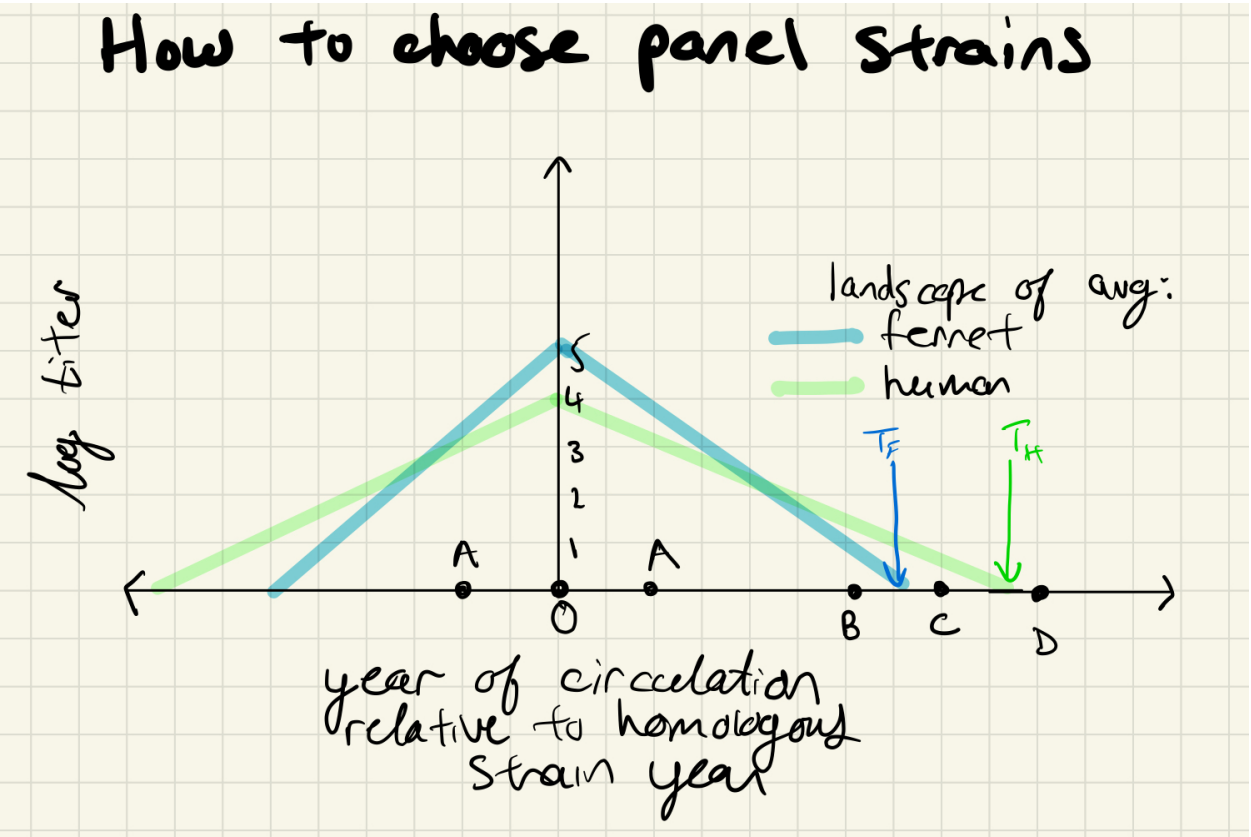

Figure 1: Idealized antigenic landscapes for ferrets and humans. The x-axis represents the temporal distance (years) between the homologous and test strain, and the y-axis represents the observed log titer.

Definitions

- T_f - Ferret threshold. Temporal distance (years) from homologous strain at which ferrets are expected to lose cross-reactivity.
- T_h - Human threshold. Temporal distance at which humans are expected to lose cross-reactivity.

We would want to include at least the following strains in the panel:

- (0) – Homologous strain
- {A} - Strain(s) temporally close to the homologous strain. (To help characterize the steepness of the landscape).
- {B} - Strains(s) just inside the ferret threshold, T_f.
- {C} - Strains(s) between the ferret and human threshold.
- {D} - Strains(s) just outside the human threshold.
- Panel strains in the set {0, A, B} should almost always have measurable titers and can characterize landscape width, steepness, and height in ferrets and humans.
- Panel strains in {C} are expected to have measurable titers in most humans, but few ferrets. Differences in cross-reactivity to {C} allow us to measure changes in ferret landscape breadth over time, and differences between ferrets and humans at the same timepoint. Ideally, {C} should contain more than one strain.
- Some humans and no ferrets are expected to show titers to {D}. {D} Helps us measure the boundary of human cross-reactivity, and to measure changes with time, or dose in human cross-reactivity.

1. Use publicly available data to quantify the temporal breadth of cross-reactivity in ferrets (T_f), and humans (T_h)

Ferret data

- Bedford et al. 2014 supplement - Compilation of ferret panel data from many publicly available sources.
- Fonville et al. 2016 supplement - antisera from 24 ferrets, each infected with a distinct strain, tested against a panel of 23 strains.

Human data

- Ha Nam data from Fonville et al. 2014 supplement. Data from 69 individuals tested against 23 strains. Individuals were sampled annually from 2007-2012. There were 12 PCR-confirmed infections (n=12), 36 seroconverters, and 32 individuals with no evidence of recent infection. We focus here on infections and seroconversions, and only analyze the serum sample proceeding the infection event.
- Fonville 2014 vaccine study data. Data from n=106 participants vaccinated against A/Nanchang/933/97 and n=128 vaccinated against A/Sydney/5/97.
- Fonville 2016 data from 17 children presumed to have recent primary infections, tested against a panel of 23 strains.

Plot for each dataset

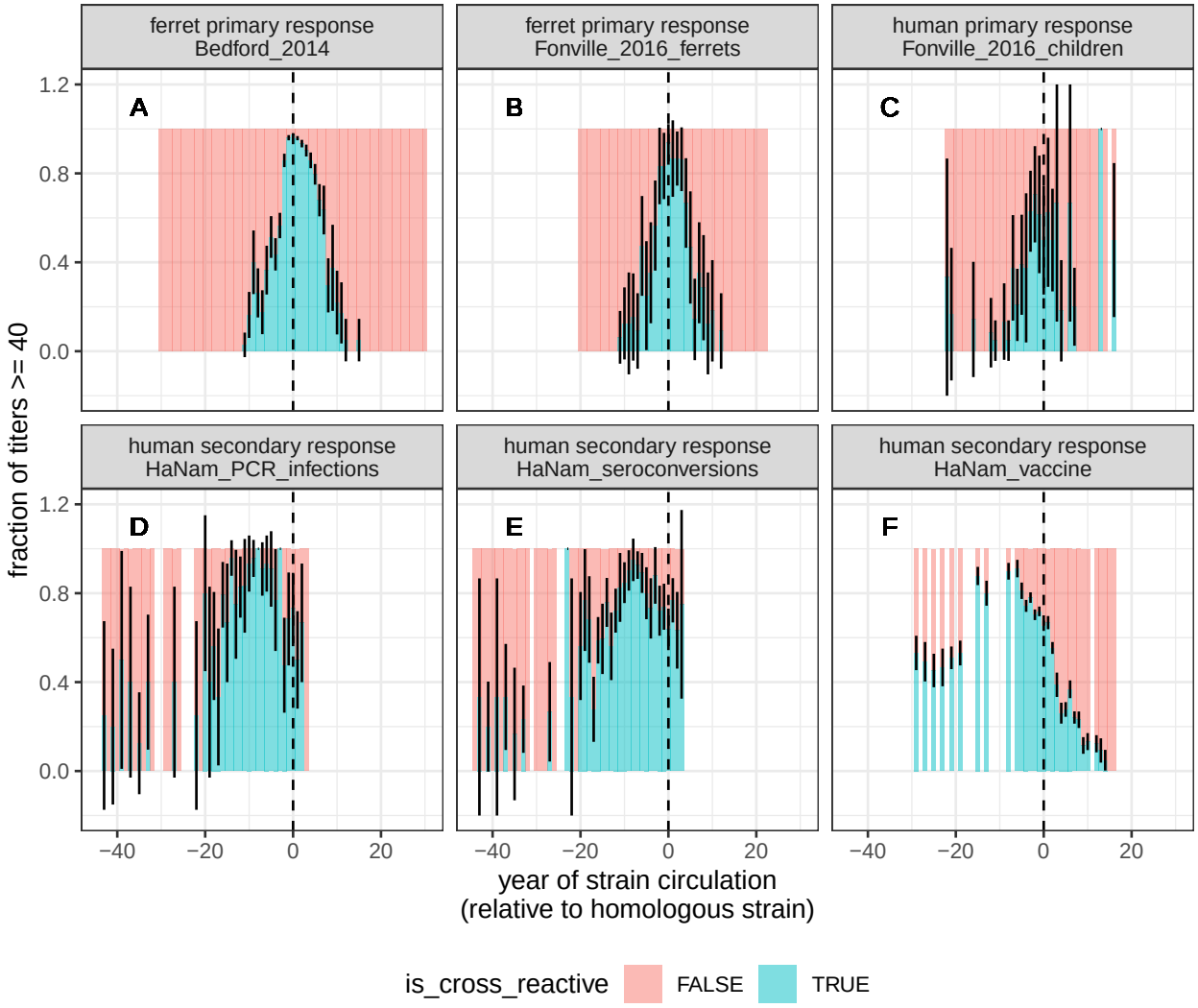

Figure 2: Cross-reactivity vs. temporal distance between the homologous strain and the test strain (years). Negative values on the x axis indicate that the test strain circulated in the past, relative to the homologous strain. The y-axis shows the fraction of titer measurements in the strain panel that were cross reactive (titer >=40). Bars show Wald confidence intervals, which is smaller for when the within-group n is large.

OBSERVATIONS:

- A, B: Strains that circulated >14 years apart rarely show cross-reactive titers in ferret HAI panels (Smith et al. 2004, Bedford et al. 2014).
- Primary responses in children (C) show slightly more temporal breadth than primary responses in ferrets (A,B).
- Secondary responses to past strains show much more temporal breadth than primary responses (D-F, vs. A-C negative x values).
- Secondary responses to future strains show only slightly greater breadth than that of primary responses (D-F, vs. A-C positive x values). However, this observation is limited by data availability. These panels contain mostly strains that circulated much earlier, not much later than the infecting strain.

IMPLICATIONS:

- We should analyze human samples collected at least 15y ago, if possible, so that we can assess cross-reactive breadth to future strains. Assessing cross-reactivity of secondary responses to past strains is not super informative due to OAS.
- From here, we need to quantify the temporal threshold at which we expect ferrets and humans to lose cross-reactivity to future strains.

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2. Estimate the temporal distance at which ferrets and humans lose cross-reactivity

Approach

Fit a logistic regression to each dataset in order to quantify the probability of cross-reactivity (P_c), as a function of temporal distance from the homologous strain, τ. Fit separate coefficients to past and future strains, and let x indicate whether the test strain circulated before or after the homologous strain. The model is:

$$logit(P_c(\tau)) = \alpha + \beta_x \tau$$

Using this logistic regression, we can estimate the threshold temporal distance, τ_x*, at which the probability that a past or future strain cross-reacts with the homologous strain. We define τ_x* as the temporal distance at which $P_c(\tau)$ falls below 0.05 in each data set.

Fit the model to each dataset

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logistic_fits = lapply(dataset_list, fit_one_logistic)
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Plot logistic fits

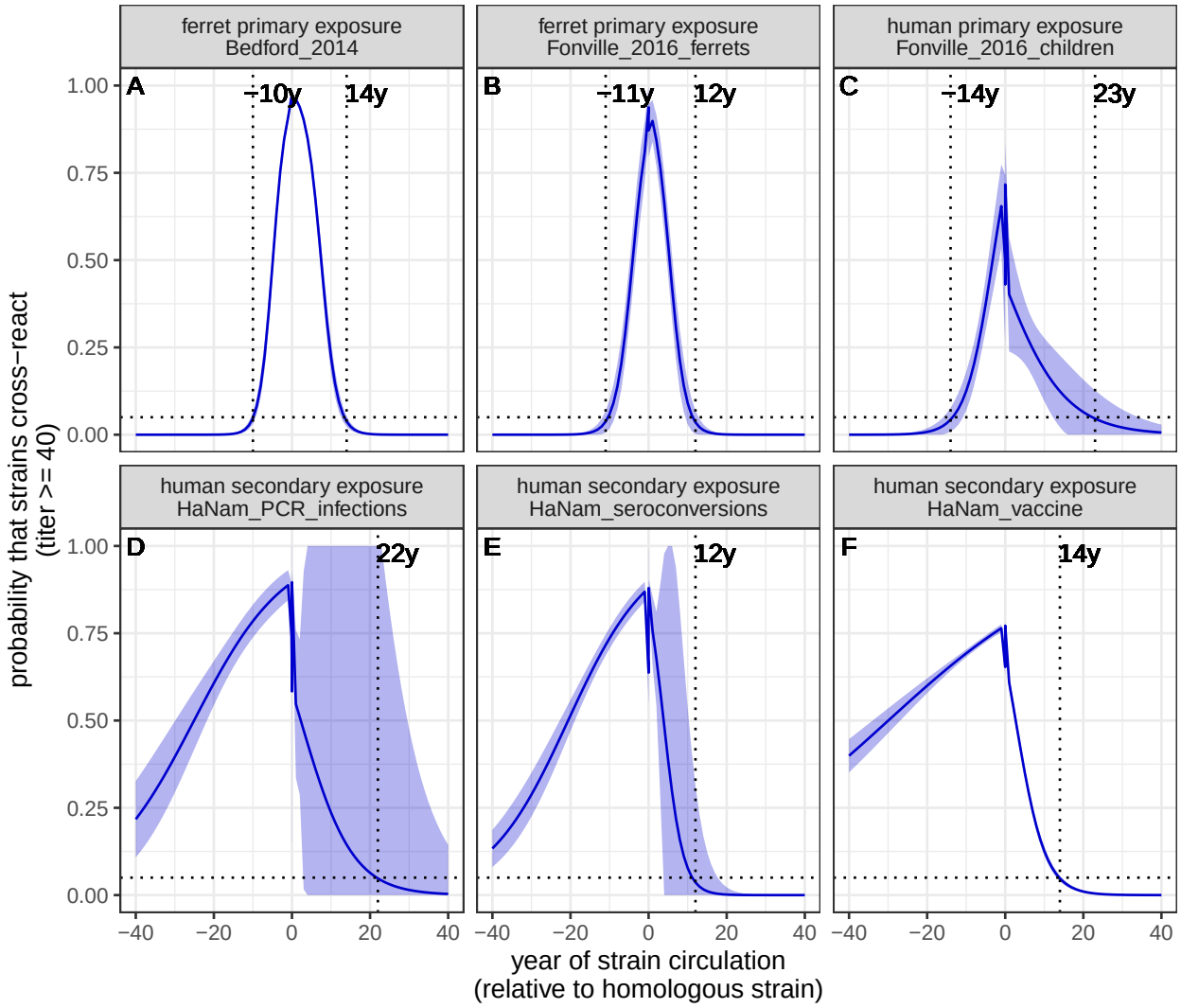

Figure 3: Logistic regression showing the probability of cross-reactivity as a function of temporal distance from the homologous strain. The dotted horizontal line shows P=0.05. The dotted vertical line and annotation shows the threshold at which the fitted probability crosses 0.05, indicating that cross-reactivity is lost.

OBSERVATIONS:

- Ferrets lose cross-reactivity to strains that circulated >14y from the homologous strain, as reported previously by Bedford et al. 2014 and Smith et al. 2004 (A,B).
- Primarily infected children (C) show somewhat greater temporal breadth than primarily infected ferrets, both to past and future strains.
- Uncertainty in the temporal breadth of cross-reactivity to future strains is highly uncertain in human antisera after infection (C, D, E), because serum samples are typically analyzed just a few years after collection, which limits the availability of titer measurements to future strains.
- The temporal breadth of cross-reactivity to past strains in secondary responses extends beyond 40y (D, E, F).
- The temporal breadth of cross-reactivity to future strains after vaccination in adults (F) is comparable to the temporal breadth of cross-reactivity in ferrets (A,B) and primarily infected children (C).

IMPLICATIONS FOR DATA COLLECTION:

- The temporal breadth of cross-reactivity to past or future strains 10-14y for primary ferret antisera.
- The temporal breadth of cross-reactivity to past or future strains is 14-23y for primary human antisera.
- The temporal breadth of cross-reactivity to future strains is c. 14y for secondary human antisera. There is no measurable limit to the breadth of cross-reactivity to past strains for secondary antisera.

Bringing this back to the conceptual outline in Fig. 1

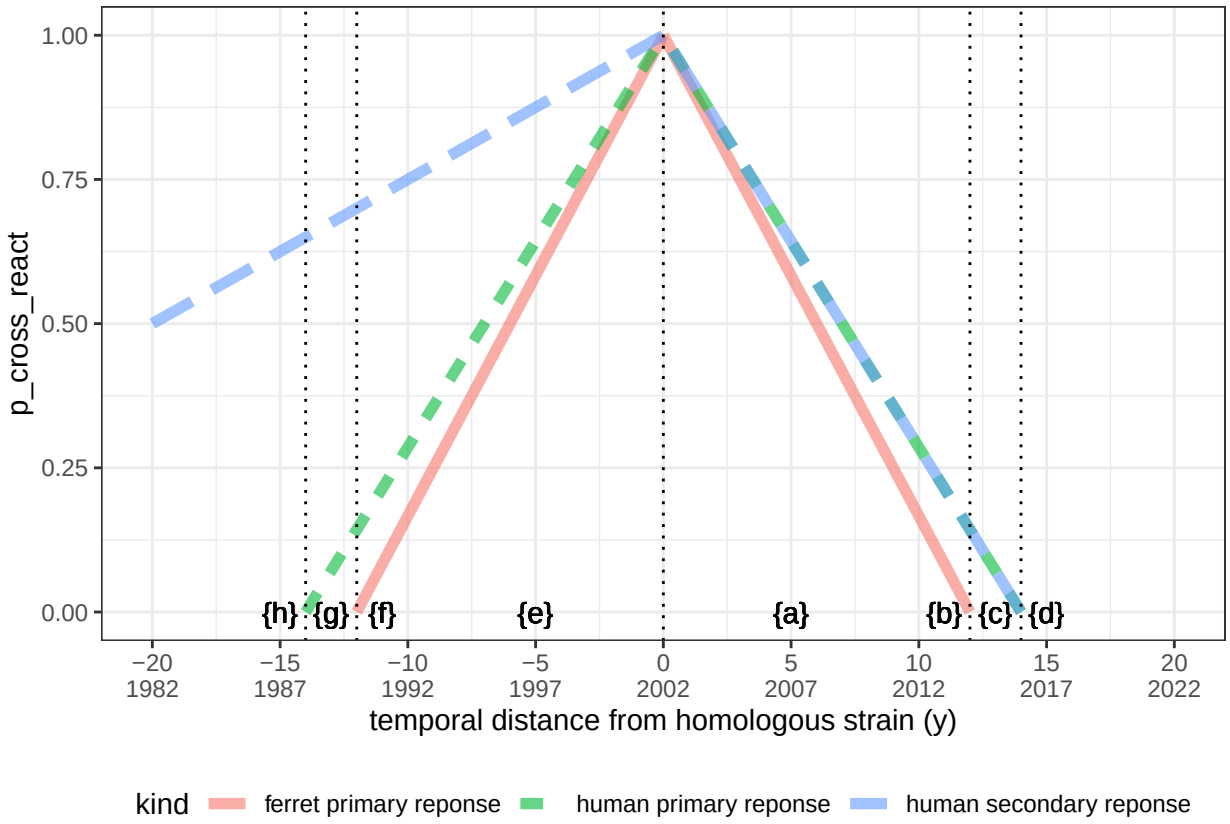

Figure 4: Version of Fig. 1 with calculated threshold distances. The x-axis shows both relative years of strain circulation [-20, 20], and calendar years, assuming that currently circulating strains are 20 years advanced from the homologous strain.

We would want to include at least the following strains in the panel:

- (0) – Homologous strain from c.2002

FUTURE STRAINS

- {a} - Strain(s) from c.2007.
- {b} - Strains(s) just inside the ferret threshold, from 2012, 2013, and 2014.
- {c} - Strains(s) between the ferret and human threshold, from 2015, 2016.
- {d} - Strains(s) just outside the human threshold, from 2017, 2018, ... present.

PAST STRAINS

- {e} - Strain(s) from c.1997.
- {f} - Strains(s) just inside the ferret threshold, from 1990, 1991, 1992.
- {g} - Strains(s) between the ferret and human threshold, from 1988, 1989.
- {h} - Strains(s) just outside the human threshold, from 1968-1987.

TOTAL:

1 homologous strain

- 9 future strains
- 9 past strains

=

19 total strains

To do tomorrow - In what years did H1N1 and H3N2 actually circulate (Flu View)

Some other issues to think about:

- If we're going to be analyzing recent H3N2 strains, HAI may not work.
- The 2009 pandemic makes things weird for H1N1.
- Should we go even further back in time to avoid these issues?