Reviewer #2: Yiming Cheng et al

This paper presents an important step forward in computer modelling the immune response to complex antigens (i.e.antigens that elicit a combined antibody and Tc response). It is a logical development of the model introduced by Celada and the late Philip Seiden in in 1992. The model has undergone a series of developments and refinements, partly in the programming and partly in its applications, which are briefly summarised here and to which the reader may need to return to gain a better understanding of the model. A key paper in this series has already appeared in Vaccine (2000). Helpfully, potential users of the model are directed to Puzone's website designed for their use.

The importance of predictive modelling for vaccine development is generally accepted, most notably in the ongoing development and annual choice of new flu vaccine strains. Much is known about the molecular structure of the viral epitopes, and the logic of prior vaccination, but prediction of vaccine efficacy is still uncertain. Relatively little is known about (1) the quantitative effects of prior vaccination and (2) the impact of prior vaccination with strains having quantitatively different levels of cross-reactivity. This paper provides a solid theoretical basis for understanding cross-reactivity.

The quantitative studies of cross-reaction reported in figs 13-14 and 16-19 are exceptionally elegant and important. They tell us in a sense all that we need to know, and make key predictions. They are likely to elicit complementary in vivo experiments that will test the predictions made here.

In addition the paper focuses on a neglected aspect of prior vaccination, namely the relative importance of cross-reactivity mediated by antibodies and by T cells. In fact this is likely to prove most important contribution made by this paper, through demonstrating how these two components of the immune response can be expected to interact. In this area the paper makes at least two important predictions that are open to experimental test. What one hopes is that some bright spark in the flu field will read this paper, hike off to New York or Genoa for detailed instruction, and then go home to do the testing.

The presentation of "epitope" and "cross-reaction" is clear, succinct and convincing.

The important contribution made by the Perelson group is appropriately cited. Their elegant work employs an analytic model of the T cell response in HIV infection and to anti-viral therapy. The Celada-Seiden model complements rather than competes with this approach, and is in my opinion intuitively more appealing.