

**Figure S3. Model predictions of mean division numbers of dividing NK cells.** The mean division number of NK cells in the divided compartment ( $M(t)$ ) can be characterized as the product of the division rate ( $k$ ) x time (*i.e.*,  $M(t) = kt$ ). Utilizing division rates estimated from Fig. 5C and 36 h as the x-axis intercept (*i.e.*, first experimental time-point at which  $M(t)$  was nonzero), predications of mean division numbers were generated with model 3. *A*, Model predictions of mean division number of NK cells stimulated with IL-15 concentrations of 9 ng/ml (dotted line) and 50 ng/ml (dashed line) were comparable with mean division numbers calculated using precursor cohort analysis of experimental data with IL-15 concentrations of 9 ng/ml (filled diamonds) and 50 ng/ml (filled squares). These results demonstrate that the model is robust enough to predict mean NK cell division numbers at concentrations of IL-15 not used in deriving the kinetic parameters (e.g.,  $k$ ). Data shown are representative of two independent experiments. *B*, Predictions of mean NK cell division numbers were calculated for cytokine reduction experiments utilizing the assumption that the cytokine concentrations decreased linearly to the new cytokine concentration over a 12 h period following cytokine exchange. Model predictions of mean division numbers were generated for NK cells that experienced either a mock cytokine exchange (dashed line) or cytokine reduction (dotted line) to IL-15 concentrations of 3 ng/ml after an initial 48 hours of stimulation with 25 ng/ml of IL-15. These predictions compared favorably with experimental values calculated using precursor cohort analysis of both the mock cytokine exchange (filled circles) and the cytokine reduction (unfilled diamonds) experiments. Results are representative of two independent experiments.

