**Calculation of the probability that a site occupied by NKG2D is not in co-existence with a KIR molecule:**

Consider an area of L× L in the plasma membrane of an NK cell. Experiments show that KIR molecules suppress NKG2D signaling the most when NKG2D and KIR are 40nm apart (Toledo et al., Sc. Adv. 2021). The area is divided into N*l*, number of small chambers of size *l*0× *l*0 where *l*0=40nm. If a particular small chamber is occupied by NKG2D, the probability that a KIR molecule will occupy that chamber when KIRs are distributed from uniform random distribution is *p*=1/N*l* = *l*02/L2. Therefore, the probability that the chamber is not occupied by a KIR is (1-*p*). If we draw N number of KIR molecules, then the probability that the chamber is not occupied by any KIR is then q=(1-p)N=(1- *l*02/L2)N =exp(N*ln*(1- *l*02/L2)) ≈ exp(-*l*02/ξ2) where ξ=L/√N ≡ average distance between the KIRs. For a ξ=34nm which is the average distance between KIRs distributed homogeneously in the membrane of a primary NK cell, ~25% of the NKG2D molecules will not be partnered by any KIR.

**Estimated parameter for gamma distribution:**

|  |  |  |  |
| --- | --- | --- | --- |
| **T=20s** | **NKG2DL** | **a** | **b** |
| **Disjoint, Low HLA-C** |  |  |  |
|  | 20 | 4.69 | 1.21 |
|  | 40 | 8.64 | 1.32 |
|  | 100 | 18.2 | 1.44 |
|  | 150 | 24.87 | 1.54 |
|  | 200 | 27.17 | 1.45 |
|  | 300 | 31.96 | 1.58 |
|  | 400 | 34.14 | 1.6 |
| **Disjoint, High HLA-C** |  |  |  |
|  | 20 | 4.79 | 1.23 |
|  | 40 | 9.45 | 1.43 |
|  | 100 | 17.63 | 1.37 |
|  | 150 | 25.14 | 1.55 |
|  | 200 | 28.25 | 1.55 |
|  | 300 | 30.88 | 1.50 |
|  | 400 | 33.97 | 1.62 |
| **Overlap, Low HLA-C** |  |  |  |
|  | 20 | 2.41 | 1.12 |
|  | 40 | 3.84 | 1.10 |
|  | 100 | 7.26 | 1.13 |
|  | 150 | 8.67 | 1.09 |
|  | 200 | 9.31 | 1.02 |
|  | 300 | 10.83 | 1.07 |
|  | 400 | 11.68 | 1.11 |
| **Overlap, High HLA-C** |  |  |  |
|  | 20 | 2.3 | 1.41 |
|  | 40 | 2.57 | 1.01 |
|  | 100 | 4.43 | 1.01 |
|  | 150 | 6.25 | 1.17 |
|  | 200 | 6.27 | 1.01 |
|  | 300 | 8.38 | 1.23 |
|  | 400 | 7.51 | 1.07 |
|  |  |  |  |
| **Homogeneous, Low HLA-C** |  |  |  |
|  | 20 | 5.11 | 1.29 |
|  | 40 | 7.98 | 1.19 |
|  | 100 | 15.46 | 1.3 |
|  | 150 | 20.69 | 1.4 |
|  | 200 | 22.67 | 1.42 |
|  | 300 | 25.93 | 1.48 |
|  | 400 | 24.16 | 1.34 |
|  |  |  |  |
| **Homogeneous, High HLA-C** |  |  |  |
|  | 20 | 3.59 | 1.13 |
|  | 40 | 6.09 | 1.17 |
|  | 100 | 11.87 | 1.26 |
|  | 150 | 14.88 | 1.32 |
|  | 200 | 15.68 | 1.28 |
|  | 300 | 18.75 | 1.42 |
|  | 400 | 18.73 | 1.39 |
|  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **T=40s** | **NKG2DL** | **a** | **b** |
| **Disjoint, Low HLA-C** | 20 | 7.56 | 1.47 |
|  | 40 | 11.36 | 1.25 |
|  | 100 | 23.38 | 1.45 |
|  | 150 | 32.00 | 1.70 |
|  | 200 | 31.81 | 1.57 |
|  | 300 | 32.84 | 1.54 |
|  | 400 | 34.81 | 1.61 |
|  |  |  |  |
| **Disjoint, High HLA-C** | 20 | 7.59 | 1.44 |
|  | 40 | 12.14 | 1.35 |
|  | 100 | 22.97 | 1.43 |
|  | 150 | 27.57 | 1.46 |
|  | 200 | 30.89 | 1.52 |
|  | 300 | 35.16 | 1.69 |
|  | 400 | 34.55 | 1.60 |
|  |  |  |  |
| **Overlap Low HLA-C** | 20 | 3.06 | 1.11 |
|  | 40 | 5.24 | 1.13 |
|  | 100 | 9.01 | 1.13 |
|  | 150 | 11.71 | 1.24 |
|  | 200 | 13.03 | 1.26 |
|  | 300 | 11.36 | 1.08 |
|  | 400 | 13.34 | 1.26 |
|  |  |  |  |
| **Overlap high HLA-C** | 20 | 2.68 | 1.35 |
|  | 40 | 3.28 | 1.00 |
|  | 100 | 5.53 | 1.01 |
|  | 150 | 6.56 | 1.04 |
|  | 200 | 7.37 | 1.10 |
|  | 300 | 7.56 | 1.07 |
|  | 400 | 9.01 | 1.25 |
|  |  |  |  |
| **Homogeneous Low HLA-C** |  |  |  |
|  | 20 | 6.45 | 1.29 |
|  | 40 | 9.81 | 1.18 |
|  | 100 | 19.63 | 1.38 |
|  | 150 | 22.05 | 1.35 |
|  | 200 | 25.89 | 1.53 |
|  | 300 | 24.20 | 1.38 |
|  | 400 | 28.88 | 1.62 |
|  |  |  |  |
| **Homogeneous high HLA-C** |  |  |  |
|  | 20 | 4.85 | 1.23 |
|  | 40 | 8.27 | 1.24 |
|  | 100 | 13.14 | 1.19 |
|  | 150 | 17.4 | 1.4 |
|  | 200 | 17.15 | 1.31 |
|  | 300 | 18.8 | 1.41 |
|  | 400 | 17.87 | 1.31 |

TableS2 : pVav1 distributions shown in Fig3 (E-G) and Fig S1 (F-N) can be fitted by the Gamma distribution given by

: . The parameters a and b for different NKG2DL numbers, for high and low HLA-C, and for all three spatial distributions of receptors are shown above.  
In both the disjoint and homogeneous scenarios, when the NKG2L numbers increase from low to intermediate values, the parameter a increases noticeably; this reflects the low probability for small pVav1 numbers when NKG2DL numbers increase. The parameter ‘b’ controls the decline in the probability for large pVav1 numbers and shows no discernible trends. These values are used to estimate the Kullback Leibler divergence between the distributions at small and large input signal. However, for overlap clusters, there is not a significant variation in the 'a' value when employing low and high HLA. The HLA number has no discernible effect on pVav numbers for disjoint clusters; as, pVav numbers depend on the activating reactions. Notably, the 'a' value is higher for overlapping cases using low HLA compared to high HLA, primarily due to elevated pVav numbers. A higher number of HLA entities result in the dephosphorylation of more pVavs, considering a dephosphorylation rate of 10s⁻¹. On the other hand, the 'b' value does not exhibit any specific trend with the NKG2L number.