Supporting Text

Model Equations and Parameter Estimation

IFN-γ Receptor-Ligand Binding. IFN-γ binds to receptors on the macrophage surface, initiating a cascade of events leading to an increase in MHC class II expression (1). We assume that this increase is the primary mechanism by which IFN-γ facilitates antigen presentation. To represent IFN-γ receptor-ligand binding, we use the general reaction scheme ligand + receptor ↔ complex. Other processes are likely to affect the number of IFN-γ receptor-ligand complexes on the time scales of IFN-γ treatment used experimentally, 20-36 h (2, 3). Celada *et al.* (4) observed that IFN-γ levels in solution decrease 13% and 83% after 4 h in the absence and presence of macrophages, respectively, indicating that appreciable levels of IFN-γ both degrade in solution and are taken up by macrophages. Therefore, in addition to representing IFN-γ receptor-ligand binding, we also represent degradation of IFN-γ in solution and within the macrophage following uptake (Eqs. **1-3**).

$$\underset{}{dG/dt} = \underset{\text{association}}{(-k_{\text{on-IFN-}\gamma}\, G \cdot R} + \underset{\text{dissociation}}{k_{\text{off-IFN-}\gamma}\, C)}\, [n_{\text{cells}} / (N_{\text{A}}\, v_{\text{rxn}})] - \underset{\text{degradation}}{k_{\text{deg-IFN-}\gamma}\, G} \qquad \textbf{[1]}$$

$$\underset{}{dR/dt} = \underset{\text{association}}{-k_{\text{on-IFN-}\gamma}\, G \cdot R} + \underset{\text{dissociation}}{k_{\text{off-IFN-}\gamma}\, C} + \underset{\text{recycling}}{k_{\text{recyc}}\, C} \qquad \textbf{[2]}$$

$$\underset{}{dC/dt} = \underset{\text{association}}{k_{\text{on-IFN-}\gamma}\, G \cdot R} - \underset{\text{dissociation}}{k_{\text{off-IFN-}\gamma}\, C} - \underset{\text{internalization}}{k_{\text{recyc}}\, C} \qquad \textbf{[3]}$$

where G is the molar concentration of IFN-γ in the medium and R and C are the numbers of free IFN-γ receptors and IFN-γ receptor-ligand complexes on the surface of each macrophage, respectively. Values for the parameters n_{cells}, the number of macrophages to which IFN-γ is added, and v_{rxn}, the volume of the medium containing both IFN-γ and macrophages, depend on the protocol being simulated, and N_{A} is Avogadro's number. Values for $k_{\text{on-IFN-}\gamma}$ and $k_{\text{off-IFN-}\gamma}$, the association and dissociation rate constants of the IFN-γ receptor-ligand complex, can be found in the literature (5), while a value for $k_{\text{deg-IFN-}\gamma}$, the rate constant for the degradation of IFN-γ in solution, can be derived from the observed decrease in IFN-γ levels when macrophages are not present if first-order decay is assumed (4). We estimate a value for k_{recyc}, the rate constant for receptor internalization and recycling, to match the observed decrease in IFN-γ levels when macrophages are present (4), given the experimental conditions of that study. Celada *et al.* (6) found that the total number of IFN-γ receptors on the surface of the macrophage, R_{tot}, does not change over time in the presence of IFN-γ. Therefore, we assume that R_{tot} is constant, allowing either Eq. **2** or Eq. **3** to be eliminated when the formula $R_{\text{tot}} = R + C$ is used to derive an expression for either R or C. In all of our simulations, we set the initial conditions for R and C to R_{tot} and 0, respectively.

MHC Class II Transcription. The formation of IFN-γ receptor-ligand complexes on the macrophage surface activates the Jak-Stat signaling pathway, increasing CIITA expression over its basal level (1, 7). Because CIITA expression may be delayed by as

much as 2 h in response to IFN-γ (8) and this delay may contribute to the longer delay observed prior to an increase in MHC class II expression (9), we represent both CIITA and MHC class II at the mRNA and protein levels explicitly in the model (Eqs. **4-6** and **11**). To represent transcription and translation, we use the same basic formulation as Maynard Smith (10). Nascent MHC class II molecules undergo several posttranslational events, including coupling of constituent subunits to invariant chain (Ii), transport through the transGolgi network, and degradation of Ii into class II-associated invariant chain peptide (CLIP) (11). The presence of low levels of mature MHC class II molecules in unstimulated macrophages suggests that these processes occur constitutively (12). We do not distinguish these processes in our model but refer to them collectively as MHC class II protein maturation. In practice, we consider MHC class II protein maturation to be part of MHC class II translation, which we represent in our model explicitly. There is evidence that IFN-γ up-regulates MHC class II translation independent of its effect on MHC class II transcription (9). Therefore, we represent IFN-γ receptor-ligand complexes as having an effect on both processes (Eqs. **4** and **11**).

$$\underset{}{dT_1/dt} = \underset{\text{transcription}}{k_{\text{txn1}}\,(1 + \alpha\, C/R_{\text{tot}})} - \underset{\text{degradation}}{k_{\text{deg-mRNA1}}\, T_1} \qquad \textbf{[4]}$$

$$\underset{}{dP/dt} = \underset{\text{translation}}{k_{\text{tsl1}}\, T_1} - \underset{\text{degradation}}{k_{\text{deg-P}}\, P} \qquad \textbf{[5]}$$

$$\underset{}{dT_2/dt} = \underset{\text{transcription}}{k_{\text{txn2}}\, \text{P}} - \underset{\text{degradation}}{k_{\text{deg-mRNA2}}\, T_2} \qquad \textbf{[6]}$$

where T_1, P, and T_2 are levels of CIITA mRNA, CIITA protein, and MHC class II mRNA per macrophage, respectively. k_{txn1}, k_{tsl1}, and k_{txn2} are rate constants for CIITA transcription, CIITA translation, and MHC class II transcription, whereas $k_{\text{deg-mRNA1}}$, $k_{\text{deg-P}}$, and $k_{\text{deg-mRNA2}}$ are rate constants for degradation of CIITA mRNA, CIITA protein, and MHC class II mRNA, respectively. We assume that unstimulated macrophages possess steady-state levels of CIITA mRNA, CIITA protein, and MHC class II mRNA (i.e., $T_1' = 0$/h, $T_1 = T_{1,0}$, $P' = 0$/h, $P = P_0$, $T_2' = 0$, and $T_2 = T_{2,0}$ when $C = 0$ mol/liter), allowing values for k_{txn1}, k_{tsl1}, and k_{txn2} to be estimated from known values of $k_{\text{deg-mRNA1}}$, $k_{\text{deg-P}}$, and $k_{\text{deg-mRNA2}}$. The quantity C/R_{tot} represents the fraction of surface IFN-γ receptors occupied at any given time, while α is a scaling factor for CIITA transcription. We assume that the rate of CIITA transcription increases linearly with the fraction of occupied IFN-γ receptors based on receptor occupation theory (13) and observed correlation between IFN-γ receptor occupancy and tumoricidal activity in macrophages (14). The scaling factor α allows MHC class II mRNA levels in the model to match increases observed experimentally in response to IFN-γ. To find a value for α, we simulate the experimental conditions used in two studies (9, 15) and approximate values for α that most closely yield the observed maximal increases in MHC class II mRNA.

Exogenous Antigens. Exogenous antigens generally enter macrophage endosomes by pinocytosis, phagocytosis, or receptor-mediated endocytosis. Because soluble model antigens such as hen egg lysozyme are typically used to assess the ability of macrophages to present antigen *in vitro* (compare refs. 2, 3, and 16), we represent only pinocytosis in the model (Eqs. **7** and **8**). We assume that endocytosed antigens either undergo partial

degradation resulting in the production of MHC class II-binding peptides, i.e., antigen processing, or are transported to lysosomes and degraded. Although a small number of exogenous antigens may also be shunted to the MHC class I pathway (17), we do not consider the loss of antigen because of this pathway in the current model. We assume that peptides resulting from antigen processing then either bind MHC class II molecules or are transported to lysosomes and degraded (Eq. **9**). The portions of our model representing antigen processing as well as peptide-MHC class II binding are similar to those used in a simpler model by Singer and Linderman (18).

$$dA^*/dt = -(k_{\text{pino}}\, n_{\text{cells}}/\text{v}_{\text{rxn}})\, A^* - k_{\text{deg-A}^*}\, A^* \qquad \textbf{[7]}$$
(endocytosis; degradation)

$$dA/dt = (k_{\text{pino}}/v_{\text{MIIC}})\, A^* - \text{k}_{\text{deg-A}}\, A - k_{\text{lys}}\, A \qquad \textbf{[8]}$$
(endocytosis; processing; degradation)

$$dE/dt = k_{\text{deg-A}}\, A - k_{\text{on-MHC}}\, M \cdot E + k_{\text{off-MHC}}\, M_{\text{e}} - k_{\text{lys}}\, E \qquad \textbf{[9]}$$
(processing; association; dissociation; degradation)

where A^*, A, and E are molar concentrations of native antigen in the medium, native antigen in the endosomal compartments of each macrophage, and antigen-derived peptide in the endosomal compartments of each macrophage, respectively. Values for the average rate of pinocytic uptake, k_{pino}, and the total volume of the MHC class II-accessible endosomal compartments, v_{MIIC}, can be found in the literature (19, 20). The parameters n_{cells} and v_{rxn} are the same as those found in Eq. **1**. We assume that the rate constant for the degradation of native antigen in the medium, $k_{\text{deg-A}^*}$, has the same value as the rate constant for the degradation of IFN-γ in solution, $k_{\text{deg-IFN-}\gamma}$. The rate constant for antigen processing, $k_{\text{deg-A}}$, represents what is likely a group of reactions, including the unfolding of native antigen and proteolytic degradation by one or more cathepsin proteases. We derive a value for $k_{\text{deg-A}}$ based on the length of time required for macrophages to degrade 50% of internalized mannosylated BSA (21), assuming that processing of most antigens yields only one peptide capable of binding MHC class II. We also assume that all soluble materials in the endosomal lumen are delivered to MHC class II-inaccessible lysosomes with the same kinetics and that therefore a single rate constant for this process, k_{lys}, is sufficient. We derive a value for k_{lys} based on the length of time required for receptor degradation (22). The rate constants $k_{\text{on-MHC}}$ and $k_{\text{off-MHC}}$ represent association and dissociation of pMHC complexes, respectively, and are described in more detail below.

Self-Peptides. Macrophages constitutively produce a population of self-peptides capable of binding MHC class II molecules within endosomes (23). In the absence of exogenous antigens, these peptides may bind 80% or more of available MHC class II molecules (23). MHC class II-binding self-peptides are derived predominantly from transmembrane proteins including several MHC-related proteins (24). In our model, we consider both MHC-derived and non-MHC-derived self-peptides as a single population (Eq. **10**). We treat self-peptides similarly to peptides derived from exogenous antigen and assume that they either bind MHC class II molecules or are transported to lysosomes and degraded. Our treatment of self-peptides is similar to that used in a previous model by Singer and Linderman (25).

$$dS/dt = k_{\text{source}} + [k_{\text{deg-MHC}}\, (M_{\text{s}} + M_{\text{s}}^*) - k_{\text{on-MHC}}\, M \cdot S$$

$$+ \underbrace{k_{\text{off-MHC}}\, M_s}_{\text{dissociation}}] \; [1 / (N_A\, \nu_{MIIC})] - \underbrace{k_{\text{lys}}\, S}_{\text{degradation}} \qquad \textbf{[10]}$$

where S is the molar concentration of self-peptides within macrophage endosomes and M, M_s, and M_s* are the numbers of free intracellular MHC class II molecules, intracellular self-peptide-MHC class II complexes, and surface self-peptide-MHC class II complexes per macrophage, respectively. We assume that the rate of self-peptide synthesis, k_{source}, for which we did not find a value in the literature, is equal to the rate of self-peptide degradation in resting macrophages, $k_{\text{lys}}\, S_0$. An additional source term, $k_{\text{deg-MHC}}\, M_s\, [1/(N_A\, \nu_{MIIC})]$, is used to represent the replenishment of MHC-derived self-peptides that are ultimately lost when pMHC complexes are degraded. For the initial value of the endosomal self-peptide concentration, S_0, we use the steady-state value, which we did not find in the literature but approximate to be 6×10^{-4} mol/liter by solving Eq. **10** when S' = 0 mol/liter/h, $M_s = M_{s,0}$, and $M = M_0$. During simulations of hypothesis H_3 (i.e., when the value of $k_{\text{on-MHC}}$ was changed) the values of S_0 and k_{source} were recalculated accordingly. However, during simulations to determine PRCC values, all rate constants were changed independently and the values of S_0 and k_{source} were not recalculated.

MHC Class II Translation and Peptide-MHC Class II Binding. We assume that the reaction scheme peptide + MHC $\leftrightarrow$ peptide-MHC complex is accurate on the time scales of most *in vitro* experimental protocols allowing us to forego more complicated representations (e.g., those in ref. 26). We also assume that the enzyme HLA-DM is expressed at sufficiently high levels within endosomes so that dissociation of CLIP from MHC class II is not rate limiting and does not require explicit representation. In addition, because the signal sequence that localizes MHC class II to endosomes is found in the cytoplasmic domain of Ii and removed from mature forms of MHC class II, we assume that all forms of MHC class II in our model are free to be transported to and from the plasma membrane. Consistent with this assumption, peptide-free MHC class II molecules have been detected on the surface of antigen-presenting cells (27, 28). In our model, we represent MHC class II by using six variables to distinguish between intracellular and surface localizations as well as free, self-peptide-bound, and exogenous peptide-bound forms (Eqs. **11-16**).

$$dM/dt = \underbrace{k_{\text{tsl2}}\, (1 + \beta\, C/R_{\text{tot}})\, T}_{\text{translation}} - \underbrace{k_{\text{on-MHC}}\, M \cdot S}_{\text{association}} + \underbrace{k_{\text{off-MHC}}\, M_s}_{\text{dissociation}} - \underbrace{k_{\text{on-MHC}}\, M \cdot E}_{\text{association}}$$
$$+ \underbrace{k_{\text{off-MHC}}\, M_e}_{\text{dissociation}} - \underbrace{k_{\text{out}}\, M}_{\text{export}} + \underbrace{k_{\text{in}}\, M^*}_{\text{recycling}} - \underbrace{k_{\text{deg-MHC}}\, M}_{\text{degradation}} \qquad \textbf{[11]}$$

$$dM^*/dt = \underbrace{k_{\text{out}}\, M}_{\text{export}} - \underbrace{k_{\text{in}}\, M^*}_{\text{recycling}} - \underbrace{k_{\text{deg-MHC}}\, M}_{\text{degradation}} \qquad \textbf{[12]}$$

$$dM_s/dt = \underbrace{k_{\text{on-MHC}}\, M \cdot S}_{\text{association}} - \underbrace{k_{\text{off-MHC}}\, M_s}_{\text{dissociation}} - \underbrace{k_{\text{out}}\, M_s}_{\text{export}} + \underbrace{k_{\text{in}}\, M_s^*}_{\text{recycling}}$$
$$- \underbrace{k_{\text{deg-MHC}}\, M_s}_{\text{degradation}} \qquad \textbf{[13]}$$

$$dM_s^*/dt = \underbrace{k_{\text{out}}\, M_s}_{\text{export}} - \underbrace{k_{\text{in}}\, M_s^*}_{\text{recycling}} - \underbrace{k_{\text{deg-MHC}}\, M_s^*}_{\text{degradation}} \qquad \textbf{[14]}$$

$$dM_e/dt = \underbrace{k_{\text{on-MHC}}\, M \cdot P}_{\text{association}} - \underbrace{k_{\text{off-MHC}}\, M_e}_{\text{dissociation}} - \underbrace{k_{\text{out}}\, M_e}_{\text{export}} + \underbrace{k_{\text{in}}\, M_e^*}_{\text{recycling}}$$

$$\underset{\text{degradation}}{- k_{\text{deg-MHC}}\, M_e} \quad \textbf{[15]}$$

$$dM_e^*/dt = \underset{\text{export}}{k_{\text{out}}\, M_e} - \underset{\text{recycling}}{k_{\text{in}}\, M_e^*} - \underset{\text{degradation}}{k_{\text{deg-MHC}}\, M_e^*} \quad \textbf{[16]}$$

where M, M_s, and M_e are the numbers of free MHC class II proteins, self-peptide-MHC class II complexes, and exogenous peptide-MHC class II complexes within the endosomal compartments of each macrophage, respectively, and M^*, M_s^*, and M_e^* are the numbers of the same MHC class II species on the surface of each macrophage. We did not find a measurement in the literature for the rate constant representing MHC class II translation, k_{tsl2}, but derive a value by assuming that unstimulated macrophages maintain a constant total number of MHC class II proteins in the absence of exogenous antigen [i.e., $(M + M^* + M_s + M_s^*)' = 0$ mol/liter/h when $G_0 = 0$ mol/liter and $E_0 = 0$ mol/liter]. Therefore, given Eqs. **11-14**, k_{tsl2} is equal to the combined rates of MHC class II protein degradation, $k_{deg\text{-}MHC}$ $(M_0 + M^*_0 + M_{s,0} + M_s^*_0)$. We also assume that all MHC class II proteins are degraded with the same rate constant, $k_{deg\text{-}MHC}$, whose value we derive from the half-life of MHC class II proteins on the surface of cultured macrophages (29). We estimate a value for the translation scaling factor, β, in a manner similar to that used for the transcription scaling factor, α. That is, we simulate the experimental conditions used by Cullell-Young *et al.* who observed a maximum increase of 37-fold in the MHC class II protein levels of macrophages incubated with IFN-γ ($n_{cells} = 5 \times 10^5$, $v_{rxn} = 1 \times 10^{-3}$ liter, $G_0 = 3 \times 10^2$ units/ml $\approx 2 \times 10^{-9}$ mol/liter, ref. 9) and approximate a value for β that matches this output. We derive a value for the rate constant of MHC class II protein transport from endosomes to the plasma membrane, k_{out}, based on the length of time this process takes in cultured macrophages (between 5 and 15 min, ref. 30), assuming that 50% of the proteins are transported during this time. Cultured macrophages retain approximately one-third of their MHC class II proteins intracellularly (31), a ratio we define as p_{in}. Based on this ratio, we derive a value for the rate constant of MHC class II protein internalization from the plasma membrane, k_{in}, by assuming that $(M^*_0 + M_s^*_0) / M_{tot} = p_{in}$ where $M_{tot} = (M_0 + M^*_0 + M_{s,0} + M_s^*_0)$ and that therefore $(M^*_0 + M_s^*_0) = [(1 - p_{in}) / p_{in}] (M_0 + M_{s,0})$. We solve Eqs. **12** and **14** for the steady-state values of M^* and M_s^* which we use as initial conditions, set their sum, $k_{out} (M_0 + M_{s,0}) / (k_{in} + k_{deg\text{-}MHC})$, equal to the expression for $(M^*_0 + M_s^*_0)$ above, and solve for k_{in}.

Values for the rate constants of peptide-MHC class II association and dissociation, $k_{on\text{-}MHC}$ and $k_{off\text{-}MHC}$, vary widely in the literature depending on the particular peptide being used. For example, complexes with peptides derived from OVA and myelin basic protein (MBP) dissociate in solution at rates of 3×10^{-6}/s and 4×10^{-4}/s, respectively (32, 33). By using the formula $t_{95\%} = -\ln(0.05) / [k_d (1 + L_0 / K_D)]$ where $t_{95\%}$ is the time required to reach 95% of equilibrium binding, k_d the dissociation rate constant, L_0 the initial ligand concentration, and K_D the equilibrium dissociation constant (34), we estimate $t_{95\%}$ values to be on the order of 100 and 1 h for OVA and MBP peptides, respectively, when $L_0 = K_D$. Considering that the length of time between the administration of exogenous antigen and the assay for surface pMHC complexes is on the order of 1 h in the experimental protocols of interest (2, 3), these values for $t_{95\%}$ suggest that, at least in some cases, the number of complexes does not reach equilibrium. If this is true, the choice of $k_{on\text{-}MHC}$ and

$k_{off\text{-}MHC}$ values would be important to the outcome of the simulations. However, the presence of the enzyme HLA-DM increases the dissociation rate constant of pMHC complexes by 10^4-fold (35), resulting in $t_{95\%}$ values of 1×10^{-2} and 1×10^{-4} h for OVA and MBP peptides, respectively, when $L_0 = K_D$. In both cases, the number of pMHC complexes is expected to reach equilibrium well before the conclusion of the assay. Therefore, we assume that the choice of peptide-specific $k_{on\text{-}MHC}$ and $k_{off\text{-}MHC}$ values from the literature does not significantly affect the outcome of the simulations due to the enzymatic activity of HLA-DM.

In all simulations, we set the initial conditions for the variables representing the different MHC class II species (i.e., M_0, M^*_0, $M_{s,0}$, $M_s{}^*_0$, $M_{e,0}$, and $M_e{}^*_0$) based on two ratios, p_{in} and p_{bound}, the fractions of all MHC class II that are intracellular and bound to self-peptide, respectively, in unstimulated macrophages when no exogenous antigen is present. We assume that p_{in} and p_{bound} apply to both free and peptide-bound MHC class II, so that $M_0 / (M_0 + M^*_0) = M_{s,0} / (M_{s,0} + M_s{}^*_0) = p_{in}$ and $M_{s,0} / (M_0 + M_{s,0}) = p_{bound}$. We express M^*_0, $M_s{}^*_0$, and $M_{s,0}$ in terms of M_0, the number of free endosomal MHC class II proteins, sum M_0, M^*_0, $M_s{}^*_0$, and $M_{s,0}$ to the known total number of MHC class II molecules in unstimulated macrophages (M_{tot}, ref. 31), and solve for each value.

Inclusion of *Mtb* and Its Inhibitory Effect on Intracellular Processes. We simulate the inhibitory effect of *Mtb* on various intracellular processes by multiplying the corresponding rate constant in the baseline model by the quantity $[1 - B/(K_M + B)]$, where B is the multiplicity of infection (moi, or bacteria-to-macrophage ratio) used *in vitro* and K_M is the MOI needed to inhibit a process by 50%. For simplicity we use a single value for K_M in all of our simulations and derive this value from the data of Noss *et al.* (2) who found that MHC class II transcription decreases by 20% and 80% when the infectious dose of *Mtb* is 5 and 40, respectively. We fit these data to the function $k_{inf} = k_{uninf} [1 - B/(K_M + B)]$ where k_{inf} and k_{uninf} are rate constants for a given process in infected and uninfected macrophages, respectively, resulting in a value for K_M of ≈18. To measure the effect on antigen presentation, we calculate $(M_e{}^*_{uninf} - M_e{}^*_{inf}) / M_e{}^*_{uninf}$ where $M_e{}^*_{uninf}$ and $M_e{}^*_{inf}$ are surface exogenous peptide-MHC class II levels ($M_e{}^*$) by using k_{uninf} and k_{inf}, respectively.

Parameters and Initial Conditions. Model simulations generating the figures and tables in the main text used the following parameters and initial conditions in place of the baseline parameters and initial conditions in Tables 3 and 4.

For Fig. 2. *A* and *B*, $n_{cells} = 4 \times 10^6$, $v_{rxn} = 8 \times 10^{-3}$ liter, $G_0 = 2 \times 10^{-6}$ mol/liter, $A^*_0 = 0$ mol/liter, ref. 15; α and k_{pino} were set to 200 and 1×10^{-12} liter/h, respectively. *C* and *D*, $n_{cells} = 5 \times 10^5$, $v_{rxn} = 1 \times 10^{-3}$ liter, $G_0 \approx 2 \times 10^{-9}$ mol/liter, $A^*_0 = 0$ mol/liter, ref. 9; α and k_{pino} were set to 30 and 1×10^{-12} liter/h, respectively. *E* and *F*, $n_{cells} = 5^* \times 10^6$, $v_{rxn} = 1 \times 10^{-3}$ liter, $G_0 = 0$ mol/liter, $A^*_0 \approx 1 \times 10^{-8}$ mol/liter, ref. 36; α = 30, $k_{pino} = 1 \times 10^{-12}$ liter/h, *G* and *H*, $n_{cells} = 9 \times 10^4$, $v_{rxn} = 4 \times 10^{-4}$ liter, $G_0 = 0$ mol/liter or $G_0 \approx 6 \times 10^{-11}$ mol/liter, $A^*_0 = 0$ mol/liter, $A^*_{16} = 2 \times 10^{-6}$ mol/liter, ref. 37; α = 30, $k_{pino} = 1 \times 10^{-12}$ liter/h.

For Table 1. $n_{cells} = 1 \times 10^5$, $v_{rxn} = 1 \times 10^{-3}$ liter, $G_0 = 1 \times 10^{-9}$ mol/liter, $A^*_0 = 1 \times 10^{-4}$ mol/liter; $\alpha = 30$, $k_{pino} = 1 \times 10^{-12}$ liter/h. $B = 40$. H_1, H_2, H_3, and H_4 correspond to model parameters $k_{deg\text{-}A}$, k_{tsl2}, $k_{on\text{-}MHC}$, and k_{txn2}, respectively.

For Fig. 3. *C*, *D*, and *E*, $n_{cells} = 1 \times 10^5$, $v_{rxn} = 1 \times 10^{-3}$ liter, $B = 50$, $G_0 = 0$ mol/liter, $A^*_0 = 0$ mol/liter, and $G_{24} \approx 1.3 \times 10^{-9}$ mol/liter, where subscript *n* refers to a condition at the *n*th hour of the experiment; α and k_{pino} were set to 30 and 1×10^{-12} liter/h, respectively. *F*, *G*, and *H*, $n_{cells} = 5 \times 10^4$, $v_{rxn} = 3.7 \times 10^{-4}$ liter, $B = 40$, $G_0 = 1.3 \times 10^{-10}$ mol/liter, $A^*_0 = 0$ mol/liter, $G_{22} = 0$ mol/liter, $G_{24} = 1.3 \times 10^{-10}$ mol/liter, $G_{46} = 0$ mol/liter, and $A^*_{46} = 2.0 \times 10^{-1}$ mol/liter; α and k_{pino} were set to 30 and 1×10^{-12} liter/h, respectively.

For Table 2. $n_{cells} = 1 \times 10^5$, $v_{rxn} = 1 \times 10^{-3}$ liter, $G_0 = 1 \times 10^{-9}$ mol/liter, $A^*_0 = 1 \times 10^{-4}$ mol/liter; $\alpha = 30$, $k_{pino} = 1 \times 10^{-12}$ liter/h were used as baseline values. MHC class II export, antigen concentration in medium, antigen uptake, MHC class II protein maturation, and IFN-γ stimulation of MHC class II translation correspond to model parameters k_{out}, A^*_0, k_{pino}, k_{tsl2}, and β, respectively. IFN-γ receptor-ligand binding, IFN-γ concentration in medium, MHC class II transcription, CIITA translation, and CIITA transcription correspond to model parameters $k_{on\text{-}IFN\text{-}\gamma}$, G_0, k_{txn2}, k_{tsl1}, and k_{txn1}, respectively. IFN-γ stimulation of CIITA transcription, IFN-γ degradation in solution, MHC class II degradation, CIITA protein degradation, CIITA mRNA degradation, and IFN-γ receptor-ligand dissociation correspond to model parameters α, $k_{deg\text{-}IFN\text{-}\gamma}$, $k_{deg\text{-}MHC}$, $k_{deg\text{-}P}$, $k_{deg\text{-}mRNA1}$, and $k_{off\text{-}IFN\text{-}\gamma}$, respectively.

For Fig. 4. $n_{cells} = 1 \times 10^5$, $v_{rxn} = 1 \times 10^{-3}$ liter, $B = 40$, $G_0 = 0$ mol/liter, $A^*_0 = 0$ mol/liter, $G_{24} \approx 1.3 \times 10^{-10}$ mol/liter, and $A^*_{t+24} = 1 \times 10^{-9}$ mol/liter, where subscript *n* refers to conditions at the *n*th hour of the experiment and *t* is variable; α and k_{pino} are set to 30 and 1×10^{-12} liter/h, respectively.

1. Steimle, V., Siegrist, C., Mottet, A., Lisowska-Grospierre, B. & Mach, B. (1994) *Science* **265,** 106-109.

2. Noss, E. H., Harding, C. V. & Boom, W. H. (2000) *Cell. Immunol.* **201,** 63-74.

3. Hmama, Z., Gabathuler, R., Jefferies, W. A., de Jong, G. & Reiner, N. E. (1998) *J. Immunol.* **161,** 4882-4893.

4. Celada, A., Gray, P. W., Rinderknecht, E. & Schreiber, R. D. (1984) *J. Exp. Med.* **160,** 55-75.

5. Sadir, R., Forest, E., & Lortat-Jacob, H. (1998) *J. Biol. Chem.* **273,** 10919-10925.

6. Celada, A., Allen, R., Esparza, I., Gray, P. W. & Schreiber, R. D. (1985) *J. Clin. Invest.* **76,** 2196-2205.

7. Darnell, J. E., Kerr, I. M. & Stark, G. R. (1994) *Science* **264,** 1415-1421.

8. Morris, A. C., Beresford, G. W., Mooney, M. R. & Boss, J. M. (2002) *Mol. Cell. Biol.* **22,** 4781-4791.

9. Cullell-Young, M., Barrachina, M., Lopez-Lopez, C., Gonalons, E., Lloberas, J., Concepcio, S. & Celada, A. (2001) *Immunogenetics* **53,** 136-144.

10. Maynard Smith, J. (1968) in *Mathematical Ideas in Biology*, ed. Maynard Smith, J. (Cambridge Univ. Press, New York), pp. 98-116.

11. Hudson, H. W. & Ploegh, H. L. (2002) *Exp. Cell Res.* **272,** 1-7.

12. Hume, D. A. (1985) *Immunobiology* **170,** 381-389.

13. Kenakin, T. P. (1987) in *Pharmacologic Analysis of Drug-Receptor Interaction*, ed. Kenakin, T. P. (Raven, New York), pp. 1-42.

14. Celada, A. & Schreiber, R. D. (1987) *J. Immunol.* **139,** 147-153.

15. Pai, R. K., Askew, D., Boom, W. H., & Harding, C. V. (2002) *J. Immunol.* **169,** 1326-1333.

16. Gercken, J., Pryjma, J., Ernst, M. & Flad, H. D. (1994) *Infect. Immun.* **62,** 3472-3478.

17. Yewdell, J. W., Norbury, C. C. & Bennink, J. R. (1999) *Adv. Immunol.* **73,** 1-77.

18. Singer, D. F. & Linderman, J. J. (1990) *J. Cell. Biol.* **111,** 55-68.

19. Dean, R. T. (1979) *Biochem. Soc. Trans.* **7,** 362-364.

20. Marsh, M., Griffiths, G., Dean, G. E., Mellman, I. & Helenius, A. (1986) *Proc. Natl. Acad. Sci. USA* **83,** 2899-2903.

21. Diment, S. & Stahl, P. (1985) *J. Biol. Chem.* **260,** 15311-15317.

22. Lauffenburger, D. A., Linderman, J. & Berkowitz, L. (1987) *Ann. N.Y. Acad. Sci.* **506,** 147-162.

23. Chicz, R. M., Urban, R. G., Gorga, J. C., Vignali, D. A., Lane, W. S. & Strominger, J. L. (1993) *J. Exp. Med.* **178,** 27-47.

24. Chicz, R. M., Urban, R. G., Lane, W. S., Gorga, J. C., Stern, L. J., Vignali, D. A & Strominger, J. L. (1992) *Nature* **358,** 764-768.

25. Singer, D. F. & Linderman, J. J. (1991) *J. Theor. Biol.* **151,** 385-404.

26. Beeson, C. & McConnell, H. M. (1995) *J. Am. Chem. Soc.* **117,** 10429-10433.

27. Germain, R. N. & Hendrix, L. R. (1991) *Nature* **353,** 134-139.

28. Santambrogio, L. K., Fischer, F. R., Dorf, M. E. & Stern, L. J. (1999) *Proc. Natl. Acad. Sci. USA* **96,** 15050-15055.

29. Poutsiaka, D. D., Yogeeswaran, G., Taylor, D. D. & Black, P. H. (1985) *Biochem. Biophys. Res. Commun.* **131,** 216-221.

30. Harding, C. V. & Geuze, H. J. (1993) *J. Immunol.* **151,** 3988-3998.

31. Harding, C. V. & Unanue, E. R. (1989) *J. Immunol.* **142,** 12-19.

32. Buus, S., Sette, A., Colon, S. M., Jenis, D. M. & Grey, H. M. (1986) *Cell* **47,** 1071-1077.

33. Mason, K. & McConnell, H. M. (1994) *Proc. Natl. Acad. Sci. USA* **91,** 12463-12466.

34. Lauffenburger, D. A. & Linderman, J. J. (1993) in *Receptors: Models for Binding, Trafficking, and Signaling*, eds. Lauffenburger, D. A. & Linderman, J. J. (Oxford Univ. Press, New York), pp. 9-72.

35. Weber, D. A., Evavold, B. D. & Jensen, P. E. (1996) *Science* **274,** 618-620.

36. Buus, S. & Werdelin, O. (1986) *Acta Pathol. Microbiol. Immunol. Scand. C* **94,** 17-24.

37. Delvig, A. A., Lee, J. J., Chrzanowska-Lightowlers, Z. M. A. & Robinson, J. H. (2002) *J. Leukocyte Biol.* **72,** 163-166.

38. Schnappauf, F., Hake, S. B., Carvajal, M. M., Bontron, S., Lisowska-Grospierre, B. & Steimle, V. (2003) *Eur. J. Immunol.* **33,** 2337-2347.

39. Selby, D. M., Singer, D. F., Anderson, R. W., Coligan, J. E., Linderman, J. J. & Nairn, R. (1995) *Cell Immunol.* **163,** 47-54.