Appendix A

We are interested in the conditions under which virus can increase when rare. In Appendix B, these conditions for the 2-compartment, 1-cell-type case are found by calculating the stability of the equilibrium with virions and infected cells at zero. Here, we present another approach. For the virus to increase when rare, the dominant eigenvalue of a next-generation matrix must be greater than 1 (Diekmann et al., 1990; Dobson and Foufopoulos, 2001). We first consider the case of viral migration alone (M_{ik}*, M_{ik} = 0) and then the case of cell migration alone (m_{ik} = 0).

Viral migration:

If each virion could migrate at most once, it would be possible to construct a general next-generation matrix (see, for example, Fulford et al. 2002). For our model, however, a virion can migrate any number of times before infecting a cell or being cleared, and so a true next-generation matrix would have to include terms for all possible movement patterns. To avoid this complication, we treat a migration event as if it were the start of a new generation for the migrating virion (below, we give the actual next-generation matrix for the special case of two compartments). The elements of the matrix are the expected numbers of virions produced in each compartment by a free virion in the same or a different compartment, by reproduction or migration. This matrix has the form:

$$\begin{bmatrix} \frac{\sum \beta_{j1} \nu_{j1} \hat{n}_{j1}}{\mu_1' + \sum \beta_{j1} \hat{n}_{j1} + \sum m_{1k}} & \frac{m_{12}}{\mu_1' + \sum \beta_{j1} \hat{n}_{j1} + \sum m_{1k}} & \cdots & \frac{m_{1p}}{\mu_1' + \sum \beta_{j1} \hat{n}_{j1} + \sum m_{1k}} \\ \frac{m_{21}}{\mu_2' + \sum \beta_{j2} \hat{n}_{j2} + \sum m_{2k}} & \frac{\sum \beta_{j2} \nu_{j2} \hat{n}_{j2}}{\mu_2' + \sum \beta_{j2} \hat{n}_{j2} + \sum m_{2k}} & \cdots & \frac{m_{2p}}{\mu_2' + \sum \beta_{j2} \hat{n}_{j2} + \sum m_{2k}} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{m_{p1}}{\mu_p' + \sum \beta_{jp} \hat{n}_{jp} + \sum m_{pk}} & \frac{m_{p2}}{\mu_p' + \sum \beta_{jp} \hat{n}_{jp} + \sum m_{pk}} & \cdots & \frac{\sum \beta_{jp} \nu_{jp} \hat{n}_{jp}}{\mu_p' + \sum \beta_{jp} \hat{n}_{jp} + \sum m_{pk}} \end{bmatrix}$$

In these equations, $\hat{n}_{ji} = \lambda_{ji} / \mu_{ji}$ is the equilibrium uninfected cell number for cell type *j* and compartment *i* (this is different from the value in the approximate equilibria section above), assuming that the virion and infected cell levels are zero. The diagonal terms give the number of virions produced on average in a compartment by one free virion in that compartment (when the virus is rare). The denominator is the sum of the rates of the various processes that can happen to a virion: clearance, infection of one of the cell types and migration. Of these, the only process that results in new virions (in that compartment) is infection, and the numerator is the sum of the infection rate for each cell type multiplied by the number of virions produced. The off-diagonal terms give the average number of free virions produced in one compartment (corresponding to the column number) resulting from a free virion in another compartment

(corresponding to the row number). A free virion in one compartment can directly give rise to at most one free virion in another compartment (namely itself, if it migrates there). Therefore, an off-diagonal element can also be interpreted as the probability that a virion in the source compartment migrates to the recipient compartment before being cleared, infecting a cell, or migrating to some other compartment.

The dominant eigenvalue of this matrix must be greater than 1 for the virus to increase when rare. (Since all elements are nonnegative, the dominant eigenvalue is real.) Therefore, at the boundary between virus increasing and not increasing when rare, there must be an eigenvalue equal to 1. However, it is possible to have an eigenvalue at 1 which is not the dominant eigenvalue, so this is a necessary but not sufficient condition.

The solution can be found in some special cases. One soluble case is one-way migration (1 to 2 to 3, for example). In this case, the matrix above is triangular, and therefore the eigenvalues are the diagonal elements. All are positive, and the dominant eigenvalue is the largest element. A diagonal term greater than 1 (necessary for the virus to increase when rare) means that in the corresponding compartment, the virus can increase when rare in the presence of virion outflow but no inflow.

The above matrix can also be solved for circular flow, in which the virus flows in one direction and from the last compartment back to the first (e.g., 1 to 2 to 3 to 1). In this case, the eigenvalues of the above matrix are the values of s satisfying

$$\prod_i \left(s - \frac{\sum \beta_{ji} \nu_{ji} \hat{n}_{ji}}{\mu_i' + \sum \beta_{ji} \hat{n}_{ji} + m_{i,i+1}} \right) = \prod_i \frac{m_{i,i+1}}{\mu_i' + \sum \beta_{ji} \hat{n}_{ji} + m_{i,i+1}}$$

where the summations are over cell types (j), and the products are over the compartments (i) from 1 to p, with $m_{i,i+1} = m_{p1}$ when $i=p$. [If any of the migration terms on the right is 0, the right side is 0 and the eigenvalues are the diagonal elements (the terms subtracted from s in the product at left), as they should be since this reduces to the one-way migration case above.] Setting $s = 1$ gives the condition for an eigenvalue to be equal to 1:

$$\prod_i \left[\mu_i' + m_{i,i+1} - \sum \beta_{ji} (\nu_{ji} - 1) \hat{n}_{ji} \right] = \prod_i m_{i,i+1}$$

This can be true for several different parameter sets, but the one that determines whether the virus can increase when rare is the one with all terms in square brackets positive.

More general cases, with bidirectional flows, do not lead readily to analytic results. The results above for circular flow, however, apply to a two-compartment system with bidirectional flow. In the two-compartment case, it is also possible to construct an actual next-generation matrix (rather than the one above, which uses the artificial assumption that virus migration initiates a new generation), whose dominant eigenvalue is R_0 for the virus. A virion can migrate any number of times before infecting a cell or being cleared, but with only two comparments the only possible pattern of migration is back and forth. Each element of the next-generation matrix is therefore a geometric series, with each term representing a number of round-trip migrations before infection or clearance. After evaluating these series, the next-generation matrix is

$$\begin{bmatrix} \dfrac{\left(\mu_2' + \sum \beta_{j2}\hat{n}_{j2} + m_{21}\right)\sum \beta_{j1}\nu_{j1}\hat{n}_{j1}}{D} & \dfrac{m_{12}\sum \beta_{j2}\nu_{j2}\hat{n}_{j2}}{D} \\ \dfrac{m_{21}\sum \beta_{j1}\nu_{j1}\hat{n}_{j1}}{D} & \dfrac{\left(\mu_1' + \sum \beta_{j1}\hat{n}_{j1} + m_{12}\right)\sum \beta_{j2}\nu_{j2}\hat{n}_{j2}}{D} \end{bmatrix}$$

where $D = \left(\mu_1' + \sum \beta_{j1}\hat{n}_{j1} + m_{12}\right)\left(\mu_2' + \sum \beta_{j2}\hat{n}_{j2} + m_{21}\right) - m_{12}m_{21}$. R_0 is the dominant eignevalue of this matrix, which is given by $\frac{1}{2}\left[c_{11} + c_{22} + \sqrt{(c_{11} - c_{22})^2 + 4c_{21}c_{12}}\right]$, where c_{ij} is the ij^{th} element of the above matrix. The condition for $R_0 > 1$ is that $(1 - c_{11})(1 - c_{22}) < c_{12}c_{21}$ or $c_{11} > 1$ or $c_{22} > 1$, which corresponds to that given above for the virus to increase when rare.

Cell migration alone:

As long as there is only one cell type (so all subscripts refer to compartment), we can also find the conditions under which virus can increase when rare under cell migration alone ($m_{ik} = 0$) using a next-generation matrix. With cell migration, a generation goes from an infected cell to the cells infected from virions released by the original cell. Again, we make the simplifying assumption that a migration event starts a new generation. The elements of the matrix are therefore the expected numbers of infected cells produced in each compartment (the column) by an infected cell in the same or a different compartment (the row), by reproduction or migration. This matrix has the form:

$$\begin{bmatrix} \frac{\mu_1^* \nu_1 \beta_1 \hat{n}_1}{(\mu_1^* + \sum M_{1k}^*)(\mu_1' + \beta_1 \hat{n}_1)} & \frac{M_{12}^*}{\mu_1^* + \sum M_{1k}^*} & \cdots & \frac{M_{1p}^*}{\mu_1^* + \sum M_{1k}^*} \\ \frac{M_{21}^*}{\mu_2^* + \sum M_{2k}^*} & \frac{\mu_2^* \nu_2 \beta_2 \hat{n}_2}{(\mu_2^* + \sum M_{2k}^*)(\mu_2' + \beta_2 \hat{n}_2)} & \cdots & \frac{M_{2p}^*}{\mu_2^* + \sum M_{2k}^*} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{M_{p1}^*}{\mu_p^* + \sum M_{pk}^*} & \frac{M_{p2}^*}{\mu_p^* + \sum M_{pk}^*} & \cdots & \frac{\mu_p^* \nu_p \beta_p \hat{n}_p}{(\mu_p^* + \sum M_{pk}^*)(\mu_p' + \beta_p \hat{n}_p)} \end{bmatrix}$$

In these equations, $\hat{n}_i$ is the equilibrium uninfected cell number for compartment *i*, assuming that the virion and infected cell levels are zero. The diagonal terms give the number of infected cells produced on average in a compartment by one infected cell in that compartment (when the virus is rare). This is the product of the probability that the cell dies before migrating [$\mu_i^* / (\mu_i^* + \sum M_{ik}^*)$], the number of virions produced if it so dies (ν_i), and the probability that a free virion infects a new cell before being cleared [$\beta_i \hat{n}_i / (\mu_i' + \beta_i \hat{n}_i)$]. The off-diagonal terms give the average number of infected cells produced in one compartment (corresponding to the column number) resulting from an infected cell in another compartment (corresponding to the row number). This is just the probability that an infected cell migrates from the row to the column compartment before dying or migrating elsewhere.

Again, the dominant eigenvalue of this matrix determines whether the virus can increase when rare (it must be greater than 1). With one-way migration (1 to 2 to 3, for example), the matrix above is triangular, and again the dominant eigenvalue is the largest diagonal element.

The above matrix can also be solved for circular flow, in which the virus flows in one direction and from the last compartment back to the first (e.g., 1 to 2 to 3 to 1). In this case, the eigenvalues of the above matrix are the values of *s* satisfying

$$\prod_i \left(s - \frac{\mu_i^* \nu_i \beta_i \hat{n}_i}{(\mu_i^* + M_{i,i+1}^*)(\mu_i' + \beta_i \hat{n}_i)} \right) = \prod_i \frac{M_{i,i+1}^*}{\mu_i^* + M_{i,i+1}^*}$$

where the products are over the compartments (*i*) from 1 to *p*, with the migration out of compartment *p* going to compartment 1. Setting *s* = 1 gives the condition for an eigenvalue to be equal to 1:

$$\prod_i \left(1 + \frac{M^*_{i,i+1}}{\mu^*_i} - \frac{\nu_i \beta_i \hat{n}_i}{\mu_i' + \beta_i \hat{n}_i} \right) = \prod_i \frac{M^*_{i,i+1}}{\mu^*_i}$$

This can be true for several different parameter sets, but the one that determines whether the virus can increase when rare is the one with all terms in parentheses positive.

In the two-compartment case, it is also possible to construct an actual next-generation matrix (rather than the one above, which uses the artificial assumption that cell migration initiates a new generation), whose dominant eigenvalue is R_0 for the virus. In this case, a generation is from free virion to free virion (the cell to cell generation above was necessary to use the assumption that migration starts a new generation, since it is the cells that migrate). So the ij^{th} element of the matrix is the expected number of virions in the next generation in compartment j resulting from a virion in compartment i.

The diagonal elements are the expected number of virions in the next generation in a compartment resulting from a virion in the same compartment. This virion production first requires that the virion infects a cell before being cleared (and the cell can be of any type). If it does, it can produce new virions in the source compartment if the cell dies before migrating, or if the infected cell makes any number of round trips to the other compartment and back before dying. The expected number of virions produced is the sum (over all events) of the product of the probability of the event and the number of virions produced.

The probability that the virion infects a cell of type j before being cleared is $\nu_{ji} \beta_{ji} \hat{n}_{ji} \big/ (\mu_i' + \sum \beta_{li} \hat{n}_{li})$ where l in the summation indicates cell type. The probability that the cell then dies before migrating is $\mu^*_{ji} / (\mu^*_{ji} + M^*_{jik})$, and in this case it produces v_{ji} free virions in the next generation. The probability that the infected cell migrates before dying is $M^*_{jik} / (\mu^*_{ji} + M^*_{jik})$, and the probability that it migrates back before dying is $M^*_{jki} / (\mu^*_{jk} + M^*_{jki})$. The probability that the infected cell makes one round trip is then $M^*_{jik} M^*_{jki} / [(\mu^*_{ji} + M^*_{jik})(\mu^*_{jk} + M^*_{jki})]$, and the probability that it makes n round trips is this quantity raised to the n^{th} power. After any number of round trips, the probability that the cell then dies before further migration is again $\mu^*_{ji} / (\mu^*_{ji} + M^*_{jik})$, and the number of virions produced is v_{ji}. The expected number of virions produced given that cell type j is infected is a thus a geometric series, with each term representing a number of round-trip migrations before cell death:

$$\frac{\beta_{ji} \hat{n}_{ji}}{\mu_i' + \sum \beta_{li} \hat{n}_{li}} \frac{\mu^*_{ji} \nu_{ji}}{\mu^*_{ji} + M^*_{jik}} \sum_{n=0}^{\infty} \left[\frac{M^*_{jik} M^*_{jki}}{(\mu^*_{ji} + M^*_{jik})(\mu^*_{jk} + M^*_{jki})} \right]^n$$

The summation is a geometric series, which is just the reciprocal of one minus the term in brackets. This gives the expected number of offspring produced by virions infecting cell type *j*. The total expected number of virions is the sum of this over all *j*, which is

$$\frac{1}{\mu_i' + \sum \beta_{li} \hat{n}_{li}} \sum_j \frac{\beta_{ji} \hat{n}_{ji} \mu_{ji}^* \nu_{ji} (\mu_{jk}^* + M_{jki}^*)}{(\mu_{ji}^* + M_{jik}^*)(\mu_{jk}^* + M_{jki}^*) - M_{jik}^* M_{jki}^*}.$$

The off-diagonal elements are found similarly, with the main difference being that there must be at least one migration for a virion in one compartment to give rise to virions in another compartment. Therefore, the next-generation matrix is.

$$\begin{bmatrix} \frac{1}{\mu_1' + \sum \beta_{l1} \hat{n}_{l1}} \sum \frac{\beta_{j1} \nu_{j1} \hat{n}_{j1} \mu_{j1}^* (\mu_{j2}^* + M_{j21}^*)}{D_j} & \frac{1}{\mu_1' + \sum \beta_{l1} \hat{n}_{l1}} \sum \frac{\beta_{j1} \nu_{j1} \hat{n}_{j1} \mu_{j2}^* M_{j12}^*}{D_j} \\ \frac{1}{\mu_2' + \sum \beta_{l2} \hat{n}_{l2}} \sum \frac{\beta_{j2} \nu_{j2} \hat{n}_{j2} \mu_{j1}^* M_{j21}^*}{D_j} & \frac{1}{\mu_2' + \sum \beta_{l2} \hat{n}_{l2}} \sum \frac{\beta_{j2} \nu_{j2} \hat{n}_{j2} \mu_{j2}^* (\mu_{j1}^* + M_{j12}^*)}{D_j} \end{bmatrix}$$

where $D_j = (\mu_{j1}^* + M_{j12}^*)(\mu_{j2}^* + M_{j21}^*) - M_{j12}^* M_{j21}^*$ and the sums are over the variable appearing in the summand (*l* or *j*, which both represent cell types). R_0 is the dominant eigenvalue of this matrix, which is given by $\frac{1}{2}\left[c_{11} + c_{22} + \sqrt{(c_{11} - c_{22})^2 + 4c_{21}c_{12}}\right]$, where c_{ij} is the ij^{th} element of the above matrix. The condition that $R_0 > 1$ corresponds to $(1 - c_{11})(1 - c_{22}) < c_{12}c_{21}$ or $c_{11} > 1$ or $c_{22} > 1$, with the first of these actually determining the boundary. This gives a very complex expression, which can be simplified greatly if we assume that the infected cell death rates and migration rates are independent of cell type. If this is true, then D_j is independent of *j*, and so can be removed from the summation (along with some of the numerator terms). It can then be shown that the condition for increase when rare is

$$\left| \mu_1^* + M_{12}^* - \frac{\mu_1^* \sum \nu_{j1} \beta_{j1} \hat{n}_{j1}}{\mu_1' + \sum \beta_{j1} \hat{n}_{j1}} \right| \left| \mu_2^* + M_{21}^* - \frac{\mu_2^* \sum \nu_{j2} \beta_{j2} \hat{n}_{j2}}{\mu_2' + \sum \beta_{j2} \hat{n}_{j2}} \right| < M_{12}^* M_{21}^*$$

(or either of the terms in brackets negative). This is similar in form to the relation with one cell type, but required the additional assumption of equal death rates and migration rates for different infected cell types.

Appendix B

Finding conditions for initial increase when rare.

Assuming all parameters are greater than zero, the system can have two equilibria: one with all variables present, and one with only uninfected cells. The conditions for the virus to increase when rare can be found by determining the stability of the equilibrium with virus levels (virions and infected cells) equal to zero. If this equilibrium is unstable, any deviation in virion or infected cell numbers (e.g., departure from zero) will increase with time.

For the one-cell-type, two-compartment model, at this equilibrium, the Jacobian matrix (assuming the equations are arranged with uninfected cells first, then infected cells, then free virions) is

$$\left[\begin{array}{cc:cccc} -\mu_1 - M_{12} & M_{21} & 0 & 0 & -\beta_1\hat{n}_1 & 0 \\ M_{12} & -\mu_2 - M_{21} & 0 & 0 & 0 & -\beta_2\hat{n}_2 \\ \hdashline 0 & 0 & -\mu_1^* - M_{12}^* & M_{21}^* & \beta_1\hat{n}_1 & 0 \\ 0 & 0 & M_{12}^* & -\mu_2^* - M_{21}^* & 0 & \beta_2\hat{n}_2 \\ 0 & 0 & \mu_1 * \nu_1 & 0 & -\mu_1' - \beta_1\hat{n}_1 - m_{12} & m_{21} \\ 0 & 0 & 0 & \mu_2 * \nu_2 & m_{12} & -\mu_2' - \beta_2\hat{n}_2 - m_{21} \end{array}\right] \quad \text{(B1)}$$

where $\hat{n}_i$ is the equilibrium number of uninfected cells in the absence of virus for compartment *i*. For viral invasion to occur, this equilibrium must be unstable, so the above matrix must have a positive dominant eigenvalue. The above matrix is block triangular (there is a submatrix at lower left that is all 0), and therefore the eigenvalues of the Jacobian are the eigenvalues of the upper left 2×2 submatrix along with those of the lower right 4×4 submatrix. The eigenvalues of the upper left submatrix are real and negative and therefore cannot cause instability, so stability is determined by the eigenvalues of the lower right submatrix, which we will refer to as **A**.

All the off-diagonal elements of **A** are nonnegative; therefore, its dominant eigenvalue is real (Horn and Johnson, 1985, p. 506). If this eigenvalue is negative, the equilibrium with no virus is stable and the virus will not increase when rare. If the dominant eigenvalue is positive, the equilibrium is unstable and the virus will (ultimately) exponentially increase when rare. If the equilibrium is on the border of stability, the dominant eigenvalue (since it is real) must be 0. The eigenvalues of **A** are the values of *s* that satisfy $|s\mathbf{I} - \mathbf{A}| = 0$; if 0 is an eigenvalue, then $|-\mathbf{A}| = 0$. Also, since the leading coefficient of the characteristic polynomial is positive (unity), for stability the constant term (which is equal to $|-\mathbf{A}|$) must also be positive (this is a result of the Routh criterion for determining the number of polynomial roots in the

right half plane; Palm III, 1983, p. 723). Therefore, instability occurs and the virus first increases when rare when $\left|-\mathbf{A}\right|$ goes from positive to negative.

From the above Jacobian, it can be shown that $\left|-\mathbf{A}\right|$ is given by

$$\mu_1 * \mu_2 * \{[\mu_1' + m_{12} - \beta_1(\nu_1 - 1)\hat{n}_1][\mu_2' + m_{21} - \beta_2(\nu_2 - 1)\hat{n}_2] - m_{12}m_{21}\} \quad \text{(B2)}$$

for the case of viral migration alone ($M_{12}^* = M_{21}^* = M_{12} = M_{21} = 0$) and by

$$(\mu_1' + \beta_1\hat{n}_1)(\mu_2' + \beta_2\hat{n}_2)\left\{\left[\mu_1^* + M_{12}^* - \frac{\mu_1^*\nu_1\beta_1\hat{n}_1}{\mu_1' + \beta_1\hat{n}_1}\right]\left[\mu_2^* + M_{21}^* - \frac{\mu_2^*\nu_2\beta_2\hat{n}_2}{\mu_2' + \beta_2\hat{n}_2}\right] - M_{12}^*M_{21}^*\right\}. \quad \text{(B3)}$$

for the case of cell migration alone ($m_{21} = m_{12} = 0$). In (B2), each term in square brackets is the difference between the virion loss rate (due to clearance and migration out of the compartment) and the virus creation rate for the compartment, while in (B3), each term in square brackets is the difference between the infected cell loss rate (due to death and migration out of the compartment) and the infected cell creation rate for the compartment (the virion creation rate multiplied by the probability that a virion in that compartment infects a cell before it is cleared). If the infectivities or burst sizes are sufficiently low (so that the virus or infected cell creation terms are less than the virion or infected cell clearance rates), $\left|-\mathbf{A}\right|$ above is positive and the virus cannot increase when rare. If the infectivities or burst sizes are then increased, eventually the point will be reached at which

$$[\mu_1' + m_{12} - \beta_1(\nu_1 - 1)\hat{n}_1][\mu_2' + m_{21} - \beta_2(\nu_2 - 1)\hat{n}_2] = m_{12}m_{21}$$

under viral migration or

$$\left[\mu_1^* + M_{12}^* - \frac{\mu_1^*\nu_1\beta_1\hat{n}_1}{\mu_1' + \beta_1\hat{n}_1}\right]\left[\mu_2^* + M_{21}^* - \frac{\mu_2^*\nu_2\beta_2\hat{n}_2}{\mu_2' + \beta_2\hat{n}_2}\right] = M_{12}^*M_{21}^*$$

under cell migration, and beyond that point $\left|-\mathbf{A}\right| < 0$, and the virus will increase when rare. As infectivities or burst sizes increase further, eventually $\left|-\mathbf{A}\right|$ might again become positive; however this only occurs if both terms in square brackets of (B2) or (B3) are negative, which means that the virus could increase when rare in either compartment even if that compartment were exporting virus but not importing any.

Obviously, in this case the virus can increase when rare, so this second boundary does not determine the ability of the virus to increase when rare. Therefore, the condition for the virus to increase when rare under viral migration is

$$[\mu_1'+m_{12}-\beta_1(v_1-1)\hat{n}_1][\mu_2'+m_{21}-\beta_2(v_2-1)\hat{n}_2]<m_{12}m_{21}\text{, or}$$

$$\mu_1'+m_{12}-\beta_1(v_1-1)\hat{n}_1<0\text{, or}$$

$$\mu_2'+m_{21}-\beta_2(v_2-1)\hat{n}_2<0,$$

which corresponds to (8a), (8b) and (8c) in the text and

$$\left[\mu_1^*+M_{12}^*-\frac{\mu_1^*v_1\beta_1\hat{n}_1}{\mu_1'+\beta_1\hat{n}_1}\right]\left[\mu_2^*+M_{21}^*-\frac{\mu_2^*v_2\beta_2\hat{n}_2}{\mu_2'+\beta_2\hat{n}_2}\right]<M_{12}^*M_{21}^*\text{, or}$$

$$\mu_1^*+M_{12}^*<\frac{\mu_1^*v_1\beta_1\hat{n}_1}{\mu_1'+\beta_1\hat{n}_1}\text{, or}$$

$$\mu_2^*+M_{21}^*<\frac{\mu_2^*v_2\beta_2\hat{n}_2}{\mu_2'+\beta_2\hat{n}_2},$$

under cell migration, which corresponds to (9a), (9b) and (9c) in the text.

Appendix C

When migration rates are high enough so that both compartments are essentially one larger, "well-mixed" compartment, the two-compartment model should in principle condense down into a single-compartment model (as in Kelly et al., 2003), if $\mu_1 = \mu_2 = \mu$, $\mu_1^* = \mu_2^* = \mu^*$, $\beta_1 = \beta_2 = \beta$, and $\nu_1 = \nu_2 = \nu$. First, we consider viral migration alone ($m \rightarrow \infty$, with M, $M^* = 0$). Let $n_1 + n_2 = n$, $n_1^* + n_2^* = n^*$, $q_1 + q_2 = q$, $\mu_1' + \mu_2' = 2\mu'$ and $\lambda_1 + \lambda_2 = \lambda$ (so μ' is the average over the two compartments, while λ is the sum). When m gets large enough, the virion abundances equalize, so $q_1 = q_2 = q/2$. These assumptions yield:

$$\frac{dn_1}{dt} + \frac{dn_2}{dt} = \frac{dn}{dt} = \lambda - \mu n - \frac{1}{2}\beta n q$$

$$\frac{dn_1^*}{dt} + \frac{dn_2^*}{dt} = \frac{dn^*}{dt} = \frac{1}{2}\beta n q - \mu^* n^*$$

$$\frac{dq_1}{dt} + \frac{dq_2}{dt} = \frac{dq}{dt} = \mu^* \nu n^* - \mu' q - \frac{1}{2}\beta n q$$

The two-compartment model under the stated assumptions gives equations almost identical to those of the one-compartment model (equations 5-7 without the migration terms and subscripts) with the only difference being that β in the one-compartment model is replaced by $\beta/2$ in the two-compartment model. We propose that because of the separation into two compartments, the total possible number of encounters between virions and healthy cells is halved. In effect, we have doubled the total "habitat" available; if we explicitly consider compartment size (volume), this is equivalent to doubling the total volume. Thus if the infection constant is in fact equivalent to an infection constant per unit volume ($\beta = \beta'/V$, see Begon et al. 2002), doubling the volume (V) results in $\beta/2$.

The same result is obtained with multiple cell types. We again make the assumptions that various parameters are the same in the two compartments, although they can still differ by cell type: $\beta_{j1} = \beta_{j2} = \beta_j$, $\nu_{j1} = \nu_{j2} = \nu_j$, $\mu_{j1}^* = \mu_{j2}^* = \mu_j^*$ and $\mu_{j1} = \mu_{j2} = \mu_j$ for cell types j, $\mu_1 = \mu_2 = \mu$ and $\mu_1^* = \mu_2^* = \mu^*$. Then, we let $\lambda_{j1} + \lambda_{j2} = \lambda_j$ and $\mu_1' + \mu_2' = 2\mu'$ and keep track of the total numbers of uninfected and infected cells of each type, as well as the total number of virions (so that $n_j = n_{j1} + n_{j2}$, $n_j^* = n_{j1}^* + n_{j2}^*$, and $q = q_1 + q_2$). Since we assuming very high migration rates, $q_1 = q_2 = q/2$. With these assumptions, the differential equations are

$$\frac{dn_j}{dt} = \lambda_j - \mu_j n_j - \tfrac{1}{2}\beta_j n_j q$$

$$\frac{dn_j^*}{dt} = \tfrac{1}{2}\beta_j n_j q - \mu_j^* n_j^*$$

$$\frac{dq}{dt} = \sum_j \mu_j^* \nu_j n_j^* - \mu' q - \sum_j \tfrac{1}{2}\beta_j n_j q$$

These equations are the same as those for a one-compartment model (see Kelly et al., 2003), except that the values of β_j are halved.

The same equations result for the two-compartment model in which there is no virion migration but cell migration becomes infinite (M, $M^* \rightarrow \infty$, with $m = 0$). In this case, for each cell type, $n_{j1} = n_{j2}$ and $n_{j1}^* = n_{j2}^*$. To obtain the equations above, the assumption that $\beta_{j1} = \beta_{j2} = \beta_j$ is still required, and we again let $\lambda_{j1} + \lambda_{j2} = \lambda_j$, but we now also require $\mu_1' = \mu_2' = \mu'$. On the other hand, the uninfected cell death rates do not need to be equal (the average value is used for μ_j), and either the infected cell death rate or burst size must be the same in both compartments, while the average value of the other can be used. With both migration of cells and virions approaching infinity, again the same equations result, with all variables equalized between compartments. In this case, it is not necessary to assume that $\beta_{j1} = \beta_{j2}$ or that $\mu_1' = \mu_2'$ (average values can be used instead).