A touch of sleep: biophysical model of contact-mediated dormancy of archaea by viruses

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1. Introduction

Dormancy is ubiquitous in microbial systems. Examples of dormancy in microbes include bacterial persistence [1–3], microbial ‘seed banks’ [4] and starvation-dependent division [5]. Microbes that enter dormancy—whether by stochastic bet hedging or via phenotypic plasticity—may do so as an evolutionary strategy in response to uncertainty in environmental selection pressures [6–8]. Infection and lysis by viruses represents a key selection pressure in the environment. For example, Escherichia coli may enter the persistence state as a means to diminish, temporarily, the ability of viruses to eliminate a local population [9]. Persister cells are characterized by slowed or even halted growth as well as decreased susceptibility to antibiotics and viruses. Nonetheless, the transition between active growth and persistence is thought to be stochastically induced rather than to be a direct consequence of virus–host interactions.

The possibility that virus–host interactions may directly induce cell-state transformations is raised by the recent empirical findings by Bautista et al. [10]. This team studied the interactions between the archaeon Sulfolobus islandicus and the dsDNA fusellovirus Sulfolobus spindle shaped virus (SSV9). Sulfolobus islandicus is a globally distributed archaeon, commonly found in hot spring ecosystems. Sulfolobus islandicus is also a model system for studying the eco-evolutionary basis for diversity in archaea [11–15]. Bautista et al. found that ‘challenge of RJW002 (the host) with SSV9 (the virus) induced a population-wide stasis or dormancy response, where the majority of cells are viable but not actively growing’ [10, p. 2]. Dormant cells appear ‘empty’ without coherent intracellular structure in contrast to normal cells. Dormant cells can then reorganize and revert to actively growing cells. In the experiment, viruses were
introduced at low concentrations relative to that of hosts. Yet, after 24 h, nearly 100% of cells were classified as dormant [10]. The interpretation of this result is that there was an amplification in the number of dormant cells at the end of the 24 h period versus the number of viruses at the start of the experiment. Further, in a follow-up experiment, nearly 100% of cells initiated dormancy even when the host was exposed to deactivated viruses at low relative concentration. Deactivated viruses should not be able to initiate infection.

Bautista et al. [10] highlight the potential role of dormancy as a strategy to survive viral infection and lysis. These experiments also raise the possibility that contact between virus particles and hosts may be sufficient to initiate a large-scale physiological response, both at the cellular and population-scales. Here, we propose a biophysical model of virus-induced dormancy of microbial host cells. The model focuses on the early dynamics of virus–host interactions in which viruses can ‘contact’ host cells reversibly. We solve the model analytically and identify distinct qualitative regimes, including one of dormancy enhancement. In the dormancy-enhancement regime, nearly all of the target host cells enter dormancy even when there are far fewer viruses than hosts. Dormancy enhancement is robust to inclusion of cell and virus turnover. We close by considering how subsequent experimental tests may help elucidate the relative importance of viral contact, infection and cell-to-cell communication in understanding the transformation of microbial cell state.

2. Methods

We propose a nonlinear dynamics model of virus–host interactions (figure 1). This model describes the early dynamics of interactions involving viruses and hosts and the initiation of either dormancy or an active infection. Consider an environment containing susceptible cells, $S$, and free virus particles, $V$. Free viruses can contact cells forming a complex, $C$, given a diffusion-limited contact rate of $k_c$ cells/(ml·h). The use of the term ‘complex’ suggests an analogy to models of enzyme kinetics. The complex is reversible. The disassociation rate is $k_d$ cells/(ml·h), and the infection rate is $k_i$ cells/ml·h. If disassociation takes place, then the virus is released back into the environment. We assume that disassociation may also induce a cellular transformation leading to dormancy with probability $p$. If viral entry takes place, then the viral genome enters the host cell. When viruses are active, this entry can lead to an actively infected cell. When viruses are active, e.g. after exposure to ultraviolet (UV) light, then entry cannot lead to infection. The density of cells with a viral genome is denoted as $I$ in either the active or deactivated scenarios.

The dynamics of this model can be written as

\[
\begin{align*}
\frac{dS}{dt} &= \left( -k_c SV + \frac{1 - p}{C_0} V \right) \\
\frac{dC}{dt} &= k_c SV - k_i C - k_d C \\
\frac{dD}{dt} &= k_i C \\
\frac{dI}{dt} &= \frac{1}{p} k_f C \\
\frac{dV}{dt} &= -k_c SV + \frac{k_d C}{C_0} 
\end{align*}
\]

The system can be reduced in complexity. First, there is a constraint that $S_0 = S(0) + C(0) + D(0) + I(0)$, because the dynamics in the model track the transformation of an initial population of $S_0$ susceptible cells into four different states: susceptible, complex, dormant and infected. There is another constraint that $V_0 = C(t) + I(t) + V(t)$, because the dynamics track the transformation of an initial population of $V_0$ viral genomes into three different states: in free viruses, temporarily bound with cells and inside of hosts. Finally, when contact occurs rapidly, then we can use a standard assumption in enzyme kinetics theory and presume that the concentration of $C$ rapidly equilibrates (for example, see the appendix of [16]). This is a standard approach to analysing models characterized by fast–slow dynamics. Here, we assume that the change in $C$ is relatively fast when compared with other state variables. In the fast limit, then $C(t) = \frac{k_c SV}{k_c + k_i}$. This approximation is referred to as quasi-steady-state approximation.
(QSSA). Substituting the QSSA equilibrium for the concentration of the complex yields the following reduced system:
\[
\frac{dS}{dt} = -SV\left(\frac{k\, k_i + pk\, k_i}{k + k_i}\right)
\]
and
\[
\frac{dV}{dt} = -SV\left(\frac{k\, k_j}{k + k_j}\right).
\]  
(2.2)

We can then identify the following control parameters: the conditional probability of infection given contact, \(q = k_j/(k + k_j)\), the effective adsorption rate, \(\phi = qk_i\), and the ratio of dormancy induction to infection, \(\delta = pk_i/k\). Using these control parameters, we can rewrite the model as
\[
\frac{dS}{dt} = -\phi SV(1 + \delta)
\]  
(2.3)

and
\[
\frac{dV}{dt} = -\phi SV.
\]  
(2.4)

This model can be interpreted as follows. The density of susceptible hosts decreases at a rate proportional to the densities of virus and susceptible host populations (equation (2.3)). The proportionality constant is \(\phi\), the adsorption rate, multiplied by an enhancement factor of \((1 + \delta)\), where \(\delta\) is the number of dormant cells induced for each infected cell produced. The enhancement factor arises because of the fact that susceptible hosts can become infected or enter dormancy owing to interactions with viruses. The number of free viruses decreases at a rate proportional to the densities of virus and susceptible host populations (equation (2.4)). The proportionality constant in that case is \(\phi\), the adsorption rate, because that is the means by which free viruses are removed from the medium.

The model does not include birth and death of hosts, the lysis of hosts by viruses, nor the decay of virus particles. As such, the model describes early dynamics of virus–host interactions. This focus is in contrast to models of virus and host dynamics mediated by density-dependent infection and lysis, rather than by contact [17–20]. We introduce and study an extension of this model with host demography and viral decay in §3d.

3. Results

(a) Qualitative regimes of dormancy induction

The model described in equation (2.3)–(2.4) can be solved analytically (see the electronic supplementary material), yielding
\[
S(t) = \frac{\Omega}{1 + (1 + \delta)M_0 e^{-\delta t}}
\]  
(3.1)

and
\[
V(t) = \frac{M_0\Omega e^{-\delta t}}{1 + (1 + \delta)M_0 e^{-\delta t}},
\]  
(3.2)

where \(\Omega = S_0 - (1 + \delta)V_0\) and \(M_0 = V_0/S_0\). These solutions hold so long as \(\Omega \neq 0\). When \(\Omega = 0\), then
\[
S(t) = \frac{S_0}{1 + S_0\delta}
\]  
(3.3)

and
\[
V(t) = \frac{V_0}{1 + V_0\phi(1 + \delta)t}.
\]  
(3.4)

The system dynamics have qualitatively different behaviours for \(\Omega > 0\) and for \(\Omega < 0\) (table 1). Therefore, \(\Omega\) acts as a critical parameter, both in a biological and dynamical systems sense.

Recall that \((1 + \delta)V_0\) is the maximum number of hosts that can be infected or enter dormancy as a result of interactions with viruses. Therefore, when \(S_0 > (1 + \delta)V_0\), then there are enough hosts for all viruses to infect cells (\(V_0\) in total) and to catalyse \(\delta\) hosts per infected cell to enter dormancy \(\delta V_0\) in total. This is the case when \(\Omega = S_0 - (1 + \delta)V_0\) is positive. In this limit, all viruses infect a cell, whereas some hosts remain uninfected. The condition \(\Omega > 0\) represents the ‘virus-depletion’ limit. By contrast, when \(S_0 < (1 + \delta)V_0\), there are not enough hosts for all viruses to infect cells and to catalyse \(\delta\) hosts per infected cell to enter dormancy. This is the case when \(\Omega = S_0 - (1 + \delta)V_0\) is negative. In this limit, all hosts are either infected or enter dormancy, whereas the viruses remain in the system. The condition \(\Omega < 0\) represents the ‘host-depletion’ limit. The condition \(\Omega = 0\) represents the critical point dividing these two dynamical regimes (figure 2).

(b) Viruses can induce nearly all hosts to enter dormancy, even when the virus–host ratio is far less than one

Traditional analysis of virus–host interactions presupposes that entrance of viral genomes into a host is required for virus-mediated modification of host cell physiology. Here, as in traditional models, \(V_0\) represents the upper limit to the number of hosts infected by viruses (table 1). This limit holds when restricting attention to short-term dynamics before replication and lysis that releases more viruses that can initiate subsequent infections. However, in the present model, hosts can also undergo contact-mediated dormancy. When the ratio of viruses to hosts is small, i.e. the multiplicity of infection (MOI) is \(M_0 = V_0/S_0 \ll 1\), we find an unexpected outcome: nearly all of the hosts can enter dormancy even when there are far fewer viruses than hosts. In the host-depletion regime, \(\Omega < 0\), then \(D_\omega = \delta S_\omega/(1 + \delta)\). If \(\delta \gg 1\), then \(D_\omega \approx S_\omega\). This condition holds so long as the relative rates of unbinding and dormancy are high relative to infection and there are enough viruses. The critical virus density depends on \(\delta\) and is equal to \(S_0/(1 + \delta)\). For virus densities above this value, then the dormant cell fraction will have reached its maximum, because the system moves from being host-depleted to virus-depleted. The comparison of the asymptotic dormant cell fraction and infected cell fraction are shown in figure 3. As is apparent, more cells become dormant and infected with increasing titre. Yet, the balance of dormancy or infected cell fates shift with increases in \(\delta\). As \(\delta\) increases,

| variable | \(\Omega < 0\) | \(\Omega = 0\) | \(\Omega > 0\) |
|----------|---------------|---------------|---------------|
| \(S\)    | 0             | 0             | \(\Omega\)    |
| \(C\)    | 0             | 0             | 0             |
| \(D\)    | \(\delta S_0\) | \(\delta V_0\) | \(\delta V_0\) |
| \(l\)    | \(S_0\)       | \(V_0\)       | \(V_0\)       |
| \(V\)    | \(-\Omega/(1 + \delta)\) | 0 | 0 |

Table 1. Asymptotic densities of state variables given the control parameter \(\Omega = S_0 - (1 + \delta)V_0\). (The conditions \(\Omega < 0\) and \(\Omega > 0\) represents the host-depletion and virus-depletion limits. See the text for more details.)
then many dormant cells are initiated for each infected cell, whereas when $\delta$ decreases, then very few dormant cells are initiated for each infected cell. Population-wide dormancy does not emerge for entry-dependent initiation given exposure of a microbial host population to viruses at low MOI (see the electronic supplementary material, SI–II).

(c) Dynamics of dormancy induction in the archaeon *Sulfolobus islandicus*

We apply our biophysical model of contact-mediated dormancy to a recent empirical study of interactions between the archaeon *S. islandicus* and the dsDNA fusellovirus *Sulfolobus* spindle shaped virus (SSV9). In the experiment, viruses were introduced at low concentrations compared with that of hosts. In this experiment, host concentrations were measured in terms of colony-forming units, and virus concentrations were measured in terms of infectious particle counts. The ratio of viruses to hosts, $M$, was estimated to range between 0.01, given plaque-forming unit counts, and 0.1, given quantitative PCR counts. In this experiment, nearly 100% of host cells entered dormancy. Hence, there was a 10- to 100-fold increase in the conversion of host cells into a dormant state. SSV9 was then exposed to UV light to deactivate the virus population. We interpret this result to mean that exposure to a relatively small number of deactivated viruses that cannot initiate infection are sufficient to induce a population-wide dormancy response. These qualitative results are the basis for our quantitative parametrization and analysis of the model.

The governing parameters of the biophysical model are $\phi$, the adsorption rate and $\delta$, the ratio of dormancy induction to infection. Bautista et al. estimated $\phi_{\text{original}}$ to be $8.4 \times 10^{-11} \text{ ml min}^{-1}$ based on the decay of plaque-forming units. They estimated the adsorption rate using the formula $\phi_{\text{original}} = 2.3 \log(V_0/V_t)/N_0 t$, where $V_0$ is the original titre of viruses, $V_t$ is the titre at time $t$ and $N_0$ is the original titre of hosts. Conventional estimates [21] use the formula $\phi = \log(V_0/V_t)/N_0 t$, hence we downward adjust the adsorption rate to be $\phi = 2.2 \times 10^{-7} \text{ ml h}^{-1}$ (note the change in units). The effective adsorption rate is a combination of the process of diffusion-limited contact and successful infection. We estimate the diffusion-limited contact rate based on the Stokes–Einstein relation [21–23]:

$$ k_s \approx 5 \times 10^{-9} \frac{n_t}{r_v} \text{ ml h}^{-1}, $$

(3.5)

where $r_v$ is the effective radius of the virus, $n_t$ is the effective radius of the host, where the prefactor is appropriate for interactions taking place in a 78°C incubator (equivalent to 351 K) and in a medium with the viscosity of water. Assuming $n_t = 1 \mu m$ and $r_v = 0.04 \mu m$ then we predict $k_s \approx 1.2 \times 10^{-7} \text{ ml h}^{-1}$. The ratio of the diffusion-limited contact rate expected from first principles, $k_s$, and the realized adsorption rate measured in the experiment, $\phi$, can be used to estimate $q = \phi/k_s = 0.02$. In this limit, then $q \approx k_s/k_\text{ads}$, such that $\delta = p/q$.

We can explore the predicted fraction of dormant cells as a function of $\delta$. First, we analyse the ratio of dormant cells to initial viruses given variation in $p$ and $q$ (figure 4A). For $q < 1$, there is a broad range of values of $p$ such that $D_{00}/V_0 > 1$. This result means that many hosts cells could enter dormancy given low relative titre of viruses. Yet, the value of $p$, and therefore of $\delta$, remains a free parameter given the experimental tests conducted in the system. The maximum value of $\delta$ is when $p \to 1$, i.e. when the conditional probability of inducing dormancy given a reversible contact approaches 1. In this case, $\delta \to 1/0.02 = 50$. Lower values of $\delta$ are possible when $p \to 0$, i.e. when the conditional probability of inducing dormancy given a reversible contact approaches 0. In this limit, $\delta \to 0$. The experimental finding of a range between $\delta = 10$ and $\delta = 100$ fold enhancement is consistent with our finding of $\delta = 45$ and a model in which $p \to 1$ (figure 4B).

We provide another evaluation of the model by considering the timescale over which contact-mediated dormancy should take place. The appropriate timescale is predicted to be $\tau_2 = 1/(1 + \delta)V_0$. The approximate cell density for experiments in [10] was $S_0 \approx 2.5 \times 10^8 \text{ ml}^{-1}$. We assume that viruses were present at $V_0 \approx 0.02 S_0$. Using these values, we estimate $\tau_2 \approx 4 \text{ h}$. Hence, we predict a characteristic timescale for conversion of 64% of hosts, corresponding to a one-log drop in susceptible host density, in a time period of 4 h and to conversion of 87% of hosts, corresponding to a two-log drop in susceptible host density, in a time period of 8 h. We view this timescale analysis to be another confirmation of the model, given that even if the hosts initiate dormancy after contact, the dormancy ‘phenotype’ is likely to be delayed given the re-organization of intracellular dynamics. In summary, non-infectious and reversible contacts could happen sufficiently frequently so as to rapidly induce dormancy on relevant timescales of experimental observations.

(d) Host dormancy and demographic dynamics

In this section, we introduce a model variant that includes the dynamics of host recovery subsequent to exposure to viruses,
including the concurrent effects of host demographic dynamics on the emergence of population-scale dormancy

\[
\begin{align*}
\frac{dS}{dt} &= rS \left(1 - \frac{N}{K}\right) - qSV(1 + \delta) + (\gamma_D + \gamma_I) D, \\
\frac{dD}{dt} &= \phi SV - \gamma_D D - \mu D, \\
\frac{dl}{dt} &= \phi SV - \gamma_I I - \mu I, \\
and \quad \frac{dV}{dt} &= -\phi SV - \frac{dV}{dt}.
\end{align*}
\]  

(3.6)

Figure 3. Asymptotic fraction of dormant and infected cells resulting from virus-host dynamics. (a) Final dormant cell fraction as a function of the initial ratio of viruses to hosts, \(V_0/S_0\). (b) Final infected cell fraction as a function of the initial ratio of viruses to hosts, \(V_0/S_0\). As shown, the final cell-state fractions depend on \(\delta\) with qualitatively different responses as a function of the control parameter \(\Omega\). The fraction of dormant cells and infected cells increases linearly with \(V_0/S_0\) so long as \(\Omega > 0\). When \(\Omega < 0\), then the fraction of dormant and infected cells is a constant, irrespective of \(V_0/S_0\). Increases in \(\delta\) lead to a relative increase in the proportion of dormant versus infected cells. Parameters are otherwise the same as in figure 2. (Online version in colour.)

Figure 4. Ratio of the concentration of dormant cells at the end of the dynamics to the concentration of viruses at the start of the dynamics. The intensity values denote the ratio, \(D/V_0\). The solid line demarcates the boundary between ratios that exceed one (upper-left portion) and those that are less than one (remainder). (a) Population dormancy enhancement as a function of the probability of infection given contact, \(q\), and the probability of dormancy-initiation given reversal of contact, \(p\). Here, \(S_0 = 2.5 \times 10^6\) cells ml\(^{-1}\) and \(V_0 = S_0/100\). (b) Population dormancy enhancement as a function of the initial virus-host ratio, \(V_0/S_0\), and the cell fate ratio, \(\delta \approx p/q\). Key point: the number of cells that enter dormancy per virus can be much greater than 1, even if the initial virus-host ratio is much smaller than 1.

In this model, \(N(t)\) represents the total cell density, i.e. \(N = S + D + I\). Additional parameters include the cell death rate \((\mu)\), virus decay rate \((d)\), dormant cell recovery rate \((\gamma_D)\), infected cell clearance rate \((\gamma_I)\) and \(r, K\) representing net host growth rate and carrying capacity, respectively. For simplicity, we assume that dormant cell recovery rate \((\gamma_D)\) and infected cell clearance rate \((\gamma_I)\) have the same value \(\gamma\). Baseline parameter values in this extension are derived from the analysis of Bautista et al. [10] (see the electronic supplementary material, SI–III).

We numerically assess the dynamics of system given variation in the dormancy recovery rate, \(\gamma\), given \(\mu = 1/24\), i.e. a cell death rate of approximately 1 day. In addition, we fix \(d = 0.087\) h\(^{-1}\), consistent with an approximately 12 h decay constant for viruses in the media (see the electronic supplementary material, SI–III). Figure 5 shows the dynamics of dormant cells \((a)\), total cells \((b)\) and the maximum fraction...
of dormant cells (c). In all cases, the system exhibits a rapid emergence of a population-wide dormant state. This state lasts for approximately 24 h in the absence of dormancy recovery ($\gamma = 0$) and is shortened given the possibility that dormant cells recover. In all cases, the population has recovered by 72 h, such that total cell density approaches the carrying capacity, and the population is comprised largely susceptible cells. Note that the total cell population decreases before this recovery occurs, because a large fraction of cells have become dormant and do not reproduce, causing cell death to outweigh production. This cost of dormancy is also observed in the experimental work of Bautista et al. [10].

The strength of large-scale dormancy induction can be characterized in terms of the maximum fraction of dormant cells at any given point in time. This maximum fraction ranges from 0.85 to 0.98 in all model variants examined, including those with slower and faster cell death rates (figure 5). These numerical results strengthen our claim that viral contact may be sufficient to induce large-scale dormancy in a host population even when deactivated viruses are present at very low relative titre (see additional validation in the electronic supplementary material, figure S1). However, this agreement also raises the question as to whether the mechanism of large-scale dormancy over short hour periods is connected to the findings of large-scale dormancy in the asymptotic limits of the reduced model.

We evaluate this question by varying the virus–host ratio and $\delta$. For each parameter and initial condition, we find the maximum dormant cell fraction, $D_{\text{max}}$ is plotted as a function of $V_0/S_0$, for different values of $\delta$. In each case, the expected domains of behaviour from the asymptotic model are denoted in terms of $\Omega$ (b) same data as in (a), but plotted with the re-scaled variables $\bar{r}$ versus $\bar{\delta}$, where $\bar{r} = (V_0/S_0)/x_0$, $\bar{\delta} = \delta$ and $x_0 = 1/(1 + \delta)$. Note that for purposes of visualizing the collapse, only a fraction of simulation results are displayed—all results correspond to the same collapse curve. Here, the parameters of the dynamic simulations are $S_0 = 2 \times 10^6$, $\phi = 2 \times 10^{-5}$, $\mu = 1/24$, $\gamma = 1/72$, $d = 1/12$, $r = 0.23$, $K = 9 \times 10^5$, all in units of hours and ml.

Figure 5. Dormancy induction at the populate scale given host demographic dynamics. (a) Dormant cell density fraction at time $t$ with varying clearance rate $\gamma$. (b) Total cell density at time $t$ with clearance (or recovery) rate $\gamma \ln(a/b)$, the value of cell death rate $\mu$ is fixed as $\mu = 1/24(\approx 0.042)$. (c) The maximum dormant cell fraction with varying clearance rate $\gamma$, when $\mu = 0$, 0.0417, 0.0833. Here, MOI is 0.04.

Figure 6. Maximum dormancy fraction in a model with host demographics and virus decay. (a) The maximum dormant fraction, $D_{\text{max}}$ is plotted as a function of $V_0/S_0$, for different values of $\delta$. In each case, the expected domains of behaviour from the asymptotic model are denoted in terms of $\Omega$. (b) Same data as in (a), but plotted with the re-scaled variables $\bar{r}$ versus $\bar{\delta}$, where $\bar{r} = (V_0/S_0)/x_0$, $\bar{\delta} = \delta$ and $x_0 = 1/(1 + \delta)$. Note that for purposes of visualizing the collapse, only a fraction of simulation results are displayed—all results correspond to the same collapse curve. Here, the parameters of the dynamic simulations are $S_0 = 2 \times 10^6$, $\phi = 2 \times 10^{-5}$, $\mu = 1/24$, $\gamma = 1/72$, $d = 1/12$, $r = 0.23$, $K = 9 \times 10^5$, all in units of hours and ml.
(1 + δ)—just as in the asymptotic model. Second, when \( V_0 \ll S_0 \), then at most \( \delta V_0 \) of the cells will enter dormancy. Hence, we expect that the initial slope of the dormancy fraction should scale with \( \delta \)—just as in the asymptotic model. Both these features are confirmed in the dynamic model. As a result, we propose an ansatz to rescale the results of simulations in figure 6a. This rescaling corresponds to \( \tilde{y} = \max(D(t)/N(t))(1 + \delta) \), \( \tilde{x} = (1 + \delta)V_0/S_0 \). In this rescaling, the characteristic virus-to-host ratio is \( x_c = 1/(1 + \delta) \). We confirm that the dynamic simulations have the same scaling behaviour in figure 6b, including the same crossover behaviour. Crucially, the bifurcation of the asymptotic model occurs when \( \delta = 0 \), or equivalently when \( V_0/S_0 = 1/(1 + \delta) \). Hence, the bifurcation in the asymptotic model can be interpreted as a crossover condition between different regimes in the dynamic model. In summary, large-scale dormancy is a robust feature of models with and without cell and virus turnover. The common requirement is that individual virus particles contact multiple hosts prior to adsorption.

4. Discussion

We have proposed a biophysical model of host-dormancy initiated by contact with viruses. The model explicitly accounts for the possibility that viruses can contact host cells reversibly. Reversible contacts may, with some frequency, lead to induction of dormancy. Such contact-mediated dormancy at the cellular scale can be evident at the population-scale in certain limits. In particular, we predict a critical transition to a regime in which the vast majority of cells become dormant even if the initial ratio of viruses to hosts is quite small. This regime is found to be robust to a broad range of biophysically relevant parameters. This regime is also robust to the inclusion of host demographic dynamics and viral decay.

The inspiration for the model was a recent series of findings that the majority of an archaeal population could enter a stasis-like ‘dormancy’ in less than 24 h after exposure to a relatively small number of viruses [10]. The same effect was observed whether active or deactivated viruses were used. This experimental finding suggests the possibility that contact between virus particles and host surfaces induce a transformation in host phenotype. Dormant cells were unlikely to be infected and lysed by viruses. However, such dormancy comes at a cost, as residing in a dormant state for too long can lead to loss of cell viability and cell death [10]. Further work would be required to evaluate whether dormancy could be initiated independent of interactions with viruses, which would represent a form of bet hedging.

We fit our original model to the experimental host-virus system, leaving only one free parameter: the conditional probability of dormancy initiation upon a reversible contact. We predict that whenever this conditional probability is sufficiently high, then large-scale initiation of dormancy can occur even when very few cells are infected. Based on our fits, we predict rapid initiation of dormancy can take place on a timescale of 4–8 h, sufficiently fast so as to identify a dormancy phenotype among the majority of the host population in the 12–24 h period as observed. Moreover, the same model fits predicts the potential for a 50-fold enhancement in dormant cells with respect to viruses. Experiments observe higher enhancement ratios ranging from 10- to 100-fold [10]. The uncertainty is owing, in part, to challenges in quantifying infectious virus titre. Inclusion of host demographic dynamics is compatible with large-scale dormancy, albeit the dormant state is a transient feature when hosts are exposed to deactivated viruses.

There are many intracellular mechanisms by which interactions between a deactivated virus and a host can lead to dormancy. Contact may initiate a host-cell-dependent regulatory mechanism that leads to a rapid change in cellular state even without infection. There may also be additional mechanisms of relevance, e.g. cell–cell communication or release of extracellular molecules, as a means to amplify a small viral contact ‘signal’. For example, an infected cell, or cell with a deactivated viral genome in its cytoplasm or integrated into its genome, may release molecules that induce dormancy in uninfected cells. Differentiating between a contact-mediated mechanism and a communication-mediated mechanism may be facilitated by experimentally varying the relative fraction of deactivated viruses. The current contact-mediated model predicts a linear decline in dormant cells below a critical ratio of viruses to hosts (figure 3). By contrast, a communication-mediated mechanism need not exhibit such a subcritical, linear relationship. Dormancy in a small population of cells could induce large-scale population changes without further interaction with viruses. In such a model, the fraction of dormant cells may switch from very low to very high, depending on the ratio of viruses to hosts, similar to quorum sensing phenomena.

In moving forward, a number of issues remain to link the proposed early-time dynamics with long-term dynamics in this specific model system. First, nonlinear feedbacks are likely to arise in this system owing to the infection and release of viruses, at least when not previously deactivated. Second, here we assume that viruses cannot infect dormant cells. The consequences of such infections remain uncertain given that interaction between viruses and dormant cells are not fully elucidated. Finally, it is known that intracellular interactions of S. islandicus and its viruses are mediated, in part, by the CRISPR/Cas immune system. The CRISPR/Cas immune system is ubiquitous in bacteria and archaea. CRISPR/Cas enable host cells to target and degrade foreign genetic elements, including viruses [24–26]. CRISPR-mediated interactions can lead, over time, to the diversification of the host as it obtains new immune elements from the virus and to the diversification of the virus [27–29]. Linking early- to long-term dynamics will also need to confront the potential diversification of communities arising owing to contact-mediated and infection-mediated dynamics.

In summary, dormancy is a feature of organisms spanning animals to plants to microbes. The evolution of dormancy has long been thought to represent a way to maximize long-term fitness in an uncertain environment [6]. For microbes, part of the uncertainty in their fitness stems from the possibility that they may be infected and lysed by a virus. Here, we find that a biophysical mechanism of contact-initiated dormancy is consistent with observations of rapid and large-scale transformation of a host archaeal population into a dormant state by a relatively small number of viruses. This transformation occurs even when hosts are exposed to deactivated viruses. Further experiments to probe how dormancy changes with variation in virus particle density may help elucidate the underlying mechanism and yield new biological surprises. In doing so, new theoretical approaches are needed to consider the integration of
‘fast’ dynamics at contact scales with the long-term non-linear feedbacks arising from the effects of physiological transformations and infection on host and virus populations.

Competing interests. We declare we have no competing interests.

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