Modes of evolution in a parasite–host interaction: Dis-entangling factors determining the evolution of regulated fimbriation in E. coli

Domínic Chu
Computing Laboratory, University of Kent, CT2 7NF Canterbury, UK

A R T I C L E   I N F O
Article history:
Received 17 April 2008
Received in revised form 9 July 2008
Accepted 10 July 2008

Keywords:
Evolution
E. coli
Fimbriation
Virulence factors
Agent-based model

A B S T R A C T
Escherichia coli expresses type-I fimbriae; these are protrusions from the outer cell wall and have been identified as a virulence factor. They are also expressed by commensal strains of E. coli although (at any one time) by only a small proportion of the population. The orthodox interpretation of this is that fimbriation is regulated so as (i) to trigger a host-based release of nutrients in the form of inflammation signals by slightly activating host defenses and (ii) while avoiding a full scale inflammatory response. This article presents a number of computer simulations of the evolution of fimbriae to scrutinize the evolutionary plausibility of this orthodox view. It turns out that these simulations suggest a revised interpretation of the fimbriae mediated parasite–host interaction. Rather than being a passive victim the host is actively providing a niche that evolutionary favors less virulent parasites. The article closes with a number of testable predictions of this model.

© 2008 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Determining the net benefit/detriment of an interaction between two species is normally very difficult given the complexity of ecosystems and simple limitations in what can be measured. It is then often useful to analyze the system in terms of its evolution. This contribution aims to illustrate the use of individual-based models in this context; specifically it will concentrate on the evolutionary models in this context; specifically it will concentrate on the interaction between E. coli and their mammalian hosts. The key-observations motivating this article is that despite being apparently commensal, these strains continue to express virulence factors (i.e. disease causing traits) at a low level. The particular virulence factor of interest here are the so-called type-I fimbriae (see below). There is substantial evidence in the literature (summarized below) that low level expression of fimbriae causes a slight activation of host-defenses, however, without leading to a full blown inflammatory reaction that would be lethal for the parasite (i.e. the bacteria). This is normally interpreted as a strategy whereby the parasite maximizes its nutrient supply while avoiding an intolerable activation of host defense; in a sense it “milks” the naive host for nutrients by exploiting a vulnerability in its defense system. This interpretation is mainly motivated by the fact that the nutrient released by the mammalian host is an indicator of inflammatory conditions and is tightly co-regulated with the expression of fimbriae.

Type-I fimbriae are hair-like structures at the cell surface that help the cell to attach to host-cells. Fimbriae are coded for by the complex of fimAFGH genes. The expression of those is controlled by the invertible genetic element fimS which only allows expression of fimbriae if it is in the “on” orientation, but suppresses the expression of fimbriae if it is in the “off” orientation. The element fimS is located between fimE and fimB; these genes code for two recombinases that catalyze inversion of fimS. FimB mainly catalyzes the off-to-on switch, whereas FimE mostly turns fimbriation off. Note that if in the off position, fimS suppresses expression of FimE (hence FimE is auto-inhibitory) along with the fimbriae, whereas expression of FimB is mainly environmentally controlled (mediated via N-acetylneuraminic acid and GlcNAc-6P concentrations in the cytoplasm). A particular cell essentially functions as a random bit generator in the sense that environmental conditions modulate the probability for a cell to be fimbriate. Normally a population of clonal cells will be heterogeneous with respect to their fimbriation state (Chu and Blomfield (2006); van der Woude (2006); van der Woude and Bäumler (2004)).

One reason fimbriae are of high (medical) interest is that they have been identified as a virulence factor in E. coli; pathogenic strains of E. coli tend to have high levels of fimbriation, but low levels can be found even in commensal strains, where only a proportion of the population expresses fimbriae (typically around 10%) (Teng (2005); Bahrami-Mougeot et al. (2002); Connell et al. (1996). Available data on the regulation of fim and theoretical arguments (see, for example Chu and Blomfield (2006)) suggests that the regulatory mechanism of fim in commensals is optimized for rapid down-regulation of fimbriation levels in response to increasing indicators of incipient inflammatory host responses (in partic-
ular N-acetyl-neura-minic acid and GlcNAc-6P). Too high levels of fimbriation lead to a full activation of host responses resulting in the eventual extinction of the resident parasite population Sohanpal et al. (2005); El-Labany et al. (2003); Chu and Blomfield (2006); Fischer et al. (2006); Gunther et al. (2002). Moderate levels of fimbriation lead to a tolerable host response accompanied by the release of N-acetyl-neura-minic acid and GlcNAc-6P, which are signals of inflammatory processes but can be utilized as carbon sources by E. coli. The metabolic pathways of these is also co-regulated with fimbriation (although with opposite sign). The common interpretation of the biological function of fim and its regulatory circuit is that parasites try to extract nutrient from the host by activating host defenses at a low level. In a way the parasite is “milking” the host for nutrients as much as possible (see Chu (2008)) by eliciting a tolerable host response, while avoiding full (and lethal) activation of host defense mechanisms (see van der Woude and Bäumler (2004)). This interpretation of the function of fimbriation in commensals will henceforth be referred to as the “milking model.”

While the milking model seems to be well corroborated by data, it also leaves a number of questions unanswered. In particular, the milking model does not explain why the host would release nutrients thus feeding the parasites; doing so seems to come at a double cost in the form of the metabolic burden of producing the nutrients and having to tolerate a higher parasitic load. Also, there is no obvious reciprocation from the parasites. A related question is why the host has not simply evolved to be more sensitive towards colonizing pathogens? A lower threshold for full activation of host defenses would remove the resident E. coli colonies and avoid the metabolic costs of “feeding” them. Part of the answer is certainly that host responses, while lethal to the parasite, come at a fitness cost to the host. Frequent inflammatory responses (i.e. disease) would by themselves diminish the host fitness. Too high a sensitivity to low level infections is therefore not a good thing. Another aspect that is not explained by the milking model is why some strains apparently suppress their virulence factors in favor of commensalism, while others do not.

The focus of this contribution is to suggest a co-evolutionary extension to the milking model that will provide some answers to these questions. The basic assumption of this extended model is that – over evolutionary time scales – the host can modulate the internal conditions provided to the parasite and as such exert a specific selection pressure on the parasite. The main mechanism to modulate the selection pressure on resident parasites is the adjustment of the host response function, i.e. the amount of nutrient/flammation that is generated in response to the number of fimbriate cells. In this sense, by adjusting this function the host can “select for” specific parasite strategies. It should be noted here that this adjustment of the response function is itself an evolutionary effect caused by adaptive pressure on the hosts. In the remainder of this article, the term “select for” will mean this co-evolutionary niche constructing process by which the host manipulates the evolutionary trajectories of its resident parasites. The simulations presented in this model lead to the hypothesis that the host attempts to minimize its pathogenic load by providing micro-ecosystems that evolutionarily favor the suppression of bacterial virulence factors by bacteria, i.e. by actively selecting for commensal strains. This comes at the cost of “feeding” and tolerating the parasites; in order for the hypothesis to be correct this cost must be counter-balanced by the reduced rate of pathogen intrusion. This leads to a modified interpretation of fimbriae and their interaction with host defenses. Instead of seeing regulated fimbriation solely as a means to elicit nutrient release from a “naive” host, the host should be seen as actively exerting selective pressure on parasites to reduce their virulence.

This contribution describes, in Section 2, a computational model of the evolution of fimbriation under the assumption of the milking model. This model shows 3 different host response curves that there are conditions that favor parasites to evolve commensalism; see Section 3. The two main conclusions from the model (discussed in Section 4) are: (i) accurate adaptive fine-tuning of the fimbriation probabilities requires low mutation rates. If the mutation rate is too high, then the parasites cannot restrain a drive towards virulence resulting in a Muller’s ratchet scenario. (ii) The host can select for less virulent strains by increasing the slope of its response function; see Fig. 6. Taking this insight to its extreme would mean that the host should evolve a switch-like response function, i.e. not release any nutrients at all before the full activation of host defenses sets in. In Section 4 it will be argued that this means that the milking model is evolutionary implausible. An alternative interpretation, namely that hosts actively select for less virulent strains is then proposed. This strategy is constrained by the requirement that the total pay-off for “commensal” strains must be higher than for virulent ones and can as such explain why hosts release nutrients in response to parasites expressing virulence factors. This article closes with three qualitative predictions in Section 5.

2. Description of the model

This section describes an individual-based (see Casti (1997)) computer model of the evolution of fimbriation. In this model each parasite is represented by a separate data structure. Parasites are born, live, reproduce and die according to rules (to be described below); these rules are applied to all parasites and compartments simultaneously, hence time progresses in discrete steps. The environment of a parasite is a compartment (representing its host). In all simulations reported in this contribution, there were 625 compartments, but during its life (a simulated) parasite normally remains within a specific compartment. A parasite’s offspring is placed into the same compartment as the parent. Movement between compartments happens at every time step, when, with a user-defined probability a randomly chosen parasite is moved to a randomly chosen new compartment.

At every time step compartments are supplied with a certain amount of “energy” (representing nutrients found in the host environment); the amount is determined by Eq. (2). Any resource within a compartment is divided up equally between parasites; parasites accumulate energy. Once a parasite has accumulated a certain (user-defined) amount of nutrient it will reproduce with a (user-defined) probability per time step. Upon reproduction, the energy counts of both the parent and the offspring are reset to zero. Once parasites reach a certain age (counted in time-steps) they will be removed from the environment with a (user-defined) probability per time step.

Parasites can be in one of two states which will henceforth be referred to as fimbriate and afimbriate. The transition between these states is probabilistic with the switch from fimbriate to afimbriate occurring with probability

$$p_{on-off} = 1 - \frac{p_1 s p_2}{p^3 + p_1 s p_2}$$

(1)

Here the parameters $p_i$ are numbers in the interval $[0, 1]$ except $p_2$ which is a number in the interval $[0, 10]$. The switch in the opposite direction, i.e. from fimbriate to afimbriate occurs with probability $p_4$. The $p_i$ are fixed for the lifetime of a specific parasite, but the population is normally heterogeneous with respect to their $p_i$. At the beginning of the simulation parasites are initialized with random values of $p_i$. Newly created offspring will, with a certain user-defined probability, be subject to a mutation, i.e. one of its $p_i$
The evolution of such and will not be re-iterated here. will henceforth refer to the exponent of initial random parasites: 10000. probability and the population size are average values taken from simulation experiments. Each point corresponds to one simulation. Points have been taken at steady state according to the mutation probability that has been used to obtain it. The parameters of this (and all other simulations in this contribution) are: number of compartments: 625, probability per time step to die/reproduce (once the relevant conditions are met): 0.2, probability to relocate a parasite per time step: 1 , parasite life time: 40, number of initial random parasites: 10000.

will be changed by a small amount. Otherwise offspring is identical to its parent for its entire life-span.

In response to the number of fimbriate parasites individual compartments release a certain amount of nutrient determined by

\[ v = \frac{20N_f}{10^h + N_f^h} \]  

(2)

where \( N_f \) is the number of fimbriate parasites in the compartment and \( h = 1, 2, 4 \) regulates the slope of the response function (we will henceforth refer to the exponent \( h \) as “Hill-coefficient”). The factor of 20 in the numerator has been chosen to set the carrying capacity of each cell (which is important in order to control the computational costs of simulations). Whenever the amount of emitted nutrient is 10 or greater, then the entire population of the compartment in question is removed; this represents (in an idealized manner) the tolerance threshold of host-cells for pathogens. Once a compartment is empty, re-population can only happen via a chance transfer of a cell from another compartment. Since this crucial value of emitted energy is chosen to lie at the inflection point of the response curve, the maximum amount of energy obtainable is equal for all values of \( h \) which makes simulations with different slopes comparable.

3. Results

Two types of simulations are considered: (i) homogeneous non-evolving populations (i.e. the \( p_i \) are fixed and the same for all parasites) provide an indication of the behavior of the system for various parameters. For these simulations the values of the \( p_i \) were chosen by hand and the mutation probability \( \mu \) set to zero. (ii) Simulations with evolution are initialized with 10,000 random parasites. After a brief transient phase, these will quickly settle to a low population level. Since offspring is subject to mutations and there is selection in the form of the extinction of entire compartments, fitter populations may evolve after some time. The evolution of such fitter populations is indicated by a sharp increase of the population in the model; in order to simplify the language, in what follows we will refer to this evolutionary transition simply as “transition.” In all simulations considered in this article at most one such transition was observed per simulation run, i.e. evolution did not proceed in small steps but rather in one big transition.

Particularly illustrative for the behavior of the model is the population size as a function of the average fimbriation level in the population. Note that in homogeneous populations this average will only depend on the host response curve. Figs. 1–3 show for a number of simulations (both evolving and homogeneous populations) the (time-)average of a population after a transition versus the (time-)average proportion of fimbriate cells (in short, the fimbriation probability). Each point corresponds to the time-average over the last 5000 time steps of a single simulation run. Taking such an average is only meaningful if the population size has reached a steady state. In practice, whether or not \( t \) was indeed reached was judged by visual inspection. This method seems more imprecise than it actually is because the evolutionary transition happens rather suddenly and is marked by a sharp increase of the population size coupled with an adjustment of the mean fimbriation of the population. Hence determining whether or not the transition (from an unadapted to an adapted population) has taken place is unambiguous in most cases.

The results of the simulations can be summarized as follows:

(1) Higher mutation probabilities lead to more consistent outcomes, i.e. the range of observed population numbers for different runs is much larger for the lowest mutation probability (\( \mu = 0.001 \)) than for the highest one (\( \mu = 1 \)); in the latter case all results cluster in one relatively small “cloud” (see Figs. 1–3).

(2) The mechanistic details of how evolution operates in this model have been described in detail in Chu (2008) and will not be re-iterated here.
(2) Higher mutation probabilities tend to lead to worse best outcomes. For example, for $h = 1$ and a mutation probability of $\mu = 0.001$ (Fig. 1) in some runs evolution leads to a population size of around 600,000 (see Fig. 1); for the same Hill coefficient ($h = 1$) but a higher mutation probability of 0.1 the population size is just over 300,000. This qualitative dependence of the population size on the mutation rate is consistent for all values of $h$ and all mutation probabilities we considered.

(3) Steeper response curves lead to lower population sizes, at least as far as the maximum observed population is concerned. While for $h = 1$ the maximum observed population is in the region of 600,000, this is reduced to about 140,000 for $h = 2$ (Fig. 2) and below 50,000 for $h = 4$ (Fig. 3). This trend is confirmed by the results obtained by homogeneous populations without evolution.

(4) The dynamics of individual compartments depends strongly on the mutation probability. For low mutation probabilities the extinction rates are high, thus leading to a boom-and-bust dynamics, i.e. sub-populations are seeded in empty compartments, rapidly grow to a large size, trigger an inflammatory response and go extinct (data not shown). For the successful instances of the lowest mutation probability, however, the extinction rates are low and compartments have stable populations with only infrequent extinction events (data not shown).

(5) The extinction rate (measured as the slope of the cumulative number of extinction events versus time) is highest for solutions evolved for $h = 1$ and lowest for $h = 4$. The cumulative extinction curve is well approximated by a straight line, hence its slope is a measure for the “virulence” of the particular strain. Table 1 shows the average slope over all simulations with a
At first this poor performance of the evolutionary optimization technique where one would stop the optimization once the optimal point is found. Real organisms, however, cannot stop their evolution and will continuously be driven over the edge of extinction by the blind watchmaker. This effect dominates the evolutionary dynamics of the model.

A consequence of this is that steeper slopes of the response curve (i.e., higher Hill coefficients $h$) leading up to the optimal fimbriation levels make it harder for the population to increase its size. This can be seen as follows: in order to avoid accidental triggering of the host defenses (and minimize residual virulence) the evolving population needs to place itself away from the optimal point, that is it needs to keep lower than (theoretically) optimal fimbriation levels; this is reflected by the above mentioned observation that the actual fimbriation number in the simulations is much lower than the optimal one (10–30 versus an optimum of 99). The reason for this is twofold. Firstly, the population needs to guard against statistical fluctuations in the number of fimbriate cells, and secondly it needs to buffer against the adaptive pressure (described above) that drives populations to and over the edge of extinction.

While staying too close to the optimal point is dangerous for the evolving populations, staying too far away from it (i.e., keeping a lower than necessary fimbriation probability) should also be avoided. Away from the optimal point the nutrient release by the host is significantly lower offering less potential for reproduction. Hence there is a conflicting requirement of having to buffer against the adaptive pressure described above which drives populations to and over the edge of extinction.

The model presented here is highly simplified vis-à-vis the biological reference system. It would therefore be futile to make detailed numerical comparisons between the simulation results and measurements obtained from real hosts. On the other hand, simplification is not only the problem of mathematical and formal models but also their virtue. A model as complex as reality would be rather pointless and not at all helpful in understanding the nature of reality. A crucial assumption underlying the following discussion is therefore that the qualitative features of the model (i.e., the functional dependence of the host-based food release on the number of fimbriate parasites, the general shape of the host response curve, the dynamics of bacterial growth, etc.) are biologically plausible.

In the present model there is no explicit fitness measure to calculate the number of offspring of an individual; instead fitness is implicit. In what follows, the “fitness” of a parasite or the “fitness” of the colony will be a notational shortcut for the relevant size of the population, or (if referring to individual cells) the potential for high population numbers. The achievable fitness of a colony is determined by the host response curve that in effect defines the “fitness-landscape” for the parasites. The current model (as indeed the interaction between $E. coli$ and its host) rely on the efficiency of group-selection mechanisms. Within a compartment there is no fitness difference between parasites because all obtain the same amount of energy. On the other hand, in the context of this model any mutational changes are only effective at the level of the individual. The mechanism by which group selection can work in the context of this model has been discussed elsewhere (see Chu (2008)) and shall not be elaborated any further here.

Table 1

<table>
<thead>
<tr>
<th>$h$</th>
<th>$\mu = 0.001$</th>
<th>$\mu = 0.1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1511682 ± 0.1308522</td>
<td>0.2206894 ± 0.07763975</td>
</tr>
<tr>
<td>2</td>
<td>0.01122584 ± 0.00449501</td>
<td>0.1394122 ± 0.070479</td>
</tr>
<tr>
<td>4</td>
<td>0.00086 ± 0.00074</td>
<td>0.00792501 ± 0.002459366</td>
</tr>
</tbody>
</table>

These averages do not take into account those simulations where no significant adaptation was observed.

4. Discussion

The fitness-landscape clearly defines an optimal point for the parasite population to be, namely just below the inflection point of the response curve where the nutrient emission and hence achievable population number are maximal. In all simulations reported here the parameters are set such that the optimal point would be at 99 fimbriate parasites per compartment. All evolved populations fail to come even close to this optimal point, with (average) fimbriate numbers in compartments being around 10–30. Note that the energy released at these low levels is much lower than at the optimal one (10–30 versus an optimum of 99). The reason for this is twofold. Firstly, the population needs to guard against statistical fluctuations in the number of fimbriate cells, and secondly it needs to buffer against the adaptive pressure (described above) that drives populations to and over the edge of extinction.

The remaining question is whether the only benefit of a lower mutation rate is a reduced evolutionary drive towards extinction or whether there are other benefits. Fig. 4 shows a population that has evolved for 40,000 time steps with $\mu = 1$; at this point the mutation probability has been set to 0. As one would expect, the population quickly increases (by about 50% to about 60,000) when the mutation rate is reduced to zero; the population size reached after the mutation probability has been set to zero is much higher than the optimal one (10–30 versus an optimum of 99). The reason for this is twofold. Firstly, the population needs to guard against statistical fluctuations in the number of fimbriate cells, and secondly it needs to buffer against the adaptive pressure (described above) that drives populations to and over the edge of extinction.

Similarly, the effect of the mutation rate on the population number fits well with this interpretation. If the mutation rate is higher then there will be a stronger force driving populations to and beyond the edge of extinction. Hence one would expect that higher mutation rates tend to lead to more extinction events and correspondingly overall lower population numbers. This is indeed observed at least in the cases of $\mu = 0.01$ and $\mu = 0.1$; see the relevant points in Figs. 1–3. These figures also reveal a complication for the case of ultra-low mutation probabilities ($\mu = 0.001$). For these the resulting population numbers vary considerably with the random seed, with population sizes ranging from much lower than to much higher than those observed in populations with higher mutation probabilities. This suggests that at very low mutation rates evolution has difficulties providing enough variation in the population for selection to work on. On the other hand, once a population has evolved it is not subject to the same detrimental drive over the edge of extinction as populations with high $\mu$ are. Cells must therefore find the correct trade-off between their ability to explore the genotypic search space and their ability to reduce the drive towards extinction.

higher and higher levels of fimbriate parasites. Hence the landscape exerts adaptive pressure towards and beyond the optimal point; as soon as this optimum is passed, populations are wiped out. The problem evolving populations face is that they cannot “know” where the point of extinction is, as it is not indicated in the fitness landscape (except where it actually happens). Hence populations will continuously be driven towards the threshold at which point they go extinct. This marks the crucial difference to an evolutionary optimization technique where one would stop the optimization once the optimal point is found. Real organisms, however, cannot stop their evolution and will continuously be driven over the edge of extinction by the blind watchmaker. This effect dominates the evolutionary dynamics of the model.
than the one achieved with \( \mu = 1 \) and \( h = 1 \) in Fig. 2. At the same time it is lower than many population sizes achieved for the ultra-low mutation probability \( \mu = 0.001 \) in Fig. 2. This indicates that the suppression of the drive to extinction is only one factor for the higher population sizes for lower \( \mu \), and that low mutation probabilities have additional benefits; presumably they allow a more fine-grained tuning of the parameters of the fimbriation function Eq. (1). This is also re-enforced by Fig. 5, where after 40,000 time-steps the mutation rate is increased from \( \mu = 0.001 \) to \( \mu = 0.1 \). This increase leads to a decrease of the population size to about 60000, which is above the cloud of corresponding results in Fig. 2 (i.e. the population is higher).

These results lead to two preliminary conclusions. Firstly, in order to avoid an adaptive drift towards virulence, parasites need to suppress mutations in areas of the genome that impact on the switching function (in particular the regions coding for FimB and FimE). Secondly, steeper response functions are useful for the host to reduce the parasite load. This conclusion is re-enforced by Table 1 showing that (in the present model) both population sizes and overall virulence of the parasites decrease with increasing \( h \). All these suggests that the ideal shape of the response function is a step-function, i.e. no nutrient release at all before the full (and for the parasites lethal) response sets in. Note however that such an all-or-nothing response would remove the conceptual basis of the milking model. If a host response always entails annihilation of the colony, then there is nothing to be gained by commensalism.

This seems to suggest that nutrient release by the host is indeed not an adaptive feature of the host biology but an unavoidable vulnerability that is exploited by \( E. coli \). However, upon closer consideration it becomes clear that this conclusion is an artifact of the design of the model. The reason for the discrepancy between model and reality has to do with the fact that in the current model

---

**Fig. 4.** A single run: The slope of the host response is \( h = 2 \) and the mutation probability is \( \mu = 1 \). After time-step 40000 the mutation probability is reduced to 0.

**Fig. 5.** A single run: The hill coefficient is 2 and the mutation probability is 1. After time-step 40000 the mutation probability was increased from \( \mu = 0.001 \) to \( \mu = 0.1 \). The graph shows that the increased mutation probability leads to a short period of population increase, before a significant and permanent reduction in the population number.
the only way for parasites to obtain nutrient is to elicit a (small) host response. Real bacteria do not depend on voluntary nutrient release by the host (unlike the simulated parasites here) but could (for example) switch to a higher virulence, thus gaining access to new nutrient sources. Note, however, that aggressive virulence is precisely what the host wants to avoid, because this would mean that it has to frequently activate its defenses, which in turn comes at a cost.

Taking all this together leads to a new hypothesis about the evolution of fimbriation in commensals. Instead of being “milked” by their parasites, hosts are actively providing a habitat for them so as to be able to exert specific selection pressures for less virulence. The host offers nutrients in exchange for the suppression of fimbriae (and presumably other virulence factors as well; see below). Assuming commensals are selected for, they will then over time out-compete more virulent strains and thus reduce the overall load on the host’s immune system (see in this context Klemm et al. (2007) for clinical examples of the interaction of different strains of E. coli in a patient). This can work if commensal strains are: (i) fitter than virulent ones while at the same time and (ii) commensal strains lead to a reduced parasitic load for the host (i.e. both are better off). These two conditions appear to be opposed since fitness is nothing but population size and a reduction of the parasitic load means precisely to have as few parasites as possible. This contradiction is indeed only apparent, which can be seen by considering population averages over time. Virulent strains have high populations only transiently (until the host has died or eradicated the pathogens), while commensals have smaller peak populations, but can stably sustain those over longer periods and might thus in the long run be better off than pathogens. From the point of view of the host, transient but high levels of parasites are more detrimental than stable but lower level populations.

At least under the conditions realized by the model presented here, parasite populations do reduce their virulence and control their growth in order to extract nutrients from their host. In the long run commensals can be competitive, even though pathogenic populations will transiently peak at higher local (i.e. within individual compartments) population numbers. Hence, by providing nutrients to the parasites conditional upon them suppressing their virulence factors (such as fimbriae) the host positively selects for commensal strains.

The remaining questions are how much nutrient the host should provide and what the shape of the response curve should be? These two questions are closely connected but not quite the same. The shape of the response curve determines the amount of nutrient parasites receive, but only up to a scaling factor (which was arbitrarily set to 20 here). The present model cannot make any quantitative predictions, but it can identify the relevant constraints. Nutrient release comes at a cost to the host. This cost must be balanced against the benefits of avoiding more virulent parasites (i.e. when no nutrients are provided) and the cost of the residual virulence of the adapted parasites (i.e. occasional bouts of virulence of the colony). Another relevant factor is the potential benefit for the parasites if they switch to full virulence. One would expect a switch towards virulence if the host provided nutrient supply is lower than what can be gained by a pathogenic strategy. Hence, while the host would be driven towards a steeper response-curve to minimize the parasitic load, it is constrained by the requirement to retain an internal environment where commensals are more competitive than pathogens.

5. Conclusion

This contribution suggests a modified view of the evolution of fimbriation to current views on the topic. Instead of focusing on fimbriation as a way to avoid detection by host defense mechanisms, a more general co-evolutionary picture is proposed. The host actively selects for parasites that are less virulent by providing nutrients in exchange for reduced virulence.

This co-evolutionary model entails a number of qualitative predictions:

(1) One would expect the amount of N-acetylneuraminic acid released by the host to be a steep function of the number of fimbriate cells. Such a steep function would reduce both the virulence of the parasites and their overall population size. An opposing requirement, however, is to keep commensalism a viable strategy for the parasites; this will be the case if the longterm average of the population size of commensal strains is higher than that of virulent ones.
Fimbriation is only a part of larger set of virulence factors. If the revised interpretation of the evolutionary significance of fimbriation is correct, then other virulence factors in E. coli (such as pap, siderophores) are similarly down-regulated in response to host emitted nutrients, or permanently turned off.

One would expect a low mutation rate in the genes controlling the expression of fim in E. coli, because otherwise populations would have a high residual virulence (they would be driven to virulence by adaptation). Mutation rates could be tested by comparing the relevant nucleotide sequences between isolates from different commensal populations and compare variation of the fim operon. One would expect the fim gene and its regulatory regions, as well as regions controlling the expression of other virulence factors, to be well conserved. On the other hand, virulent strains would not be constrained to low mutation rates.

Acknowledgments

This work was partially funded by the EPSRC (grant number EP/F035152/1). I thank Ian Blomfield for discussions on fimbriation and its importance for the host–parasite relation.

References


Gunther, J., Snyder, J., Lockatell, V., Blomfield, I., Johnson, D., Mobley, H., 2002. Assessment of virulence of uropathogenic Escherichia coli type 1 fimbral mutants in which the invertible element is phase-locked on or off. Infection and Immunity 70, 3344–3354.


