



# Monte Carlo Simulation of Arbitrium and the Probabilistic Behavior of Bacteriophages

Huber Nieto-Chaupis<sup>(✉)</sup>

Universidad Autónoma del Perú, Panamericana Sur Km. 16.3 Villa el Salvador,  
Lima, Peru

hubernietochoaupis@gmail.com

**Abstract.** From the fact that phage takes a random decision to opt either by lysis or lysogeny, this paper has carried out a Montecarlo simulation of the attack of phage against bacteria. When it is assumed random variables along the attack, then it would produce a indecision for having lysis or lysogeny that is quantitatively seen as a small probability for both scenarios. Thus a delay emerges that is favorable to bacteria in the sense that phages might to be disorganized and destabilize because their ambition. This can also be understood as a scenario of interference by which the molecular messengers emitted by phages is abundant, so that more sub-processes together to lysis and lisogeny might be manifested. It has been assumed that messengers become negatively or positively charged, yielding to attraction or repulsion among genes. Thus, the decision for lysis and lysogeny would have a random origin in conjunction to Coulomb's forces.

**Keywords:** Arbitrium · Bacteriophage · Bayes theorem

## 1 Introduction

With the discovery of system baptized as Arbitrium by Rotem Sorek in 2017 [1], it was seen so far a progressive increasing of literature corresponding to the ways as phages are communicate each other in order to carry out a decision as to go through lysis or lysogeny. In fact, it was discovery that bacteriophage makes a kind of coordination previous to the “final assault” in hostage bacteria. Although not clear in all if these coordinations have as central purpose the saving of time or energy, the phage might be behaving as a perfect criminal microbial targeting the extermination of their prey guided by randomness to some extent, so that deterministic aspects that are unknown emerge as a interesting window whose arguments might not be falling in a biological territory but also, in aspects that are totally determined by laws of physics and probabilities. As seen in [2,3] such decision might be as a group more than individual. Nevertheless, this apparent democracy exhibits a lack of consistency about the origin and true purpose of system Arbitrium. In other words, it is not clear if it is totally random or

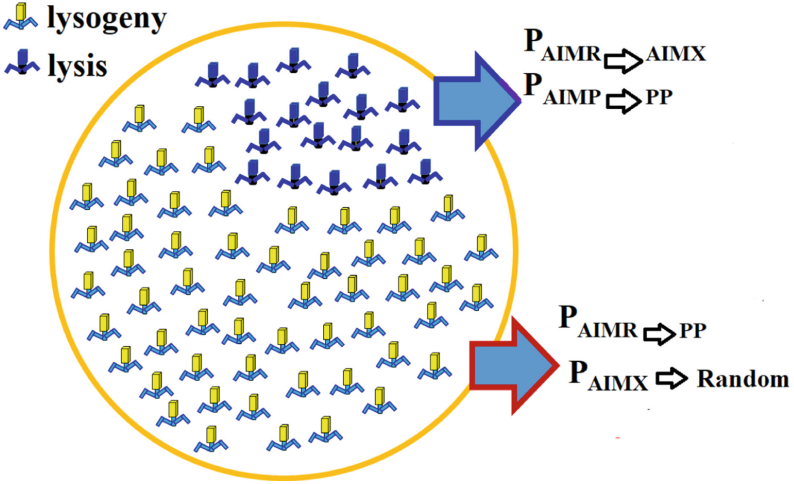
partially deterministic. In one phase of system, gen aimP is emitted so that, the accumulation of these genes in an extracellular manner to initialize the actions towards the decision might be in according to a concrete statistics. Thus, while not any manifestation of segregated peptides, then one can assign a probabilistic role at the sense that not all peptides would be received by aimP receptors along the DNA integration [4]. Despite the fact that the quorum sensing might be a very sophisticated regulatory systems, the presence of electrical factors either in phages or peptides makes the system arbitrium in one sign-dependent so that one would expect either attraction or repulsion. The case of repulsion might be a drastic scenario because peptides are displacing each other without to reach its aimR in the hijacked bacteria [5,6].

The rest of this paper is a follows: In second section, once the event of substrate depletion by a population of bacteria is defined, each subprocess is mathematically projected onto a scenario of Bayes's theorem. From this probability, some illustrative examples based in simulations are presented. Interestingly is found that the Bayesian probability is periodic in some ranges of space, fact that would trigger the idea that diffusivity and Bayes's theorem would have a short matching in space and time.

## 2 The Bayesian Interpretation

Before of going to a fully Bayesian interpretation of Arbitrium, it would be pedagogical to write in a nutshell about it [7]. In this manner the sequence can be listed as follows: (i) Phage adheres to a bacteria in order to take it as a pure hostage without any chance to be released in an independent manner. One can note that this hijacking has a only purpose: Destruction of bacteria or keep them alive to improve the phage population [8]. (ii) This adherence targets to deposit the AimR and AimP genes. It is noteworthy that AimR express the key gen AimX. (iii) When AimX is activated, the action of lysogeny is blocked out, so that lysis begins. (iv) AimP releases peptides (six amino acids long) as a form of secret communication. (v) Peptides can be taken by oligopeptide permease (OPP) transporter. Once inside hostage bacteria, AimR binds peptides so that the gene cannot activate AimX anymore. (vi) Lysogeny can be carry out. With this sequence one can define a list of probabilities: Probability of activation AimX because AimR  $P_{RX}$ . Probability of releasing peptides by AimP  $P_{PP}$ . Probability of uptake peptides by AimR  $P_{RPP}$ . In this manner, one can apply the conditional concepts of Bayes's theorem in fully relation to Arbitrium as follows: Probability for a decision of lysis:  $P_{RX} \times P_{PP}$ . Probability for lysogeny:  $1 - P_{RX} \times P_{PP}$  and the probability to confirm lysogeny:  $P_{RPP}$ . Here one can see that the sum of all probabilities both lysis and lysogeny is equal to unity. The mathematical transcription of Bayes's theorem [9] with all these probabilities can be written as (Fig. 1):

$$P_B = \frac{P_{RX} \times P_{PP}}{P_{RX} \times P_{PP} + (1 - P_{RX} \times P_{PP}) \times P_{RPP}}. \quad (1)$$



**Fig. 1.** Sketch of a scenario for Arbitrium where the option lysis is favorable. Thus the probabilities are generated in according to the conditional probability of Bayes's theorem. The main question associated to this sketch is: What is probability that a fraction of viruses take the option of lysis? The meaning of the acronyms is provided in text.

### 3 The Physics of Arbitrium

Equation 1 can be considered as a master equation in the sense that from it, various interpretations can be done. A possible is inside the territory of physics. In fact, from the fact that genes and peptides have electrical charges in their surface, then they can behave in according to well-known Coulomb's law, it is only can exist either attraction or rejection [10, 11]. In this manner and by following the observations of Sorek one can define a kind of electrical origin to the actions for each one of probabilities defined above. In this manner one can write down:

$$P_{\text{AimR} \rightarrow \text{AimX}} = P_{\text{RX}} = \frac{\beta Q_{\text{R}} Q_{\text{X}}}{d_{\text{RX}}^2} \quad (2)$$

$$P_{\text{AimP} \rightarrow \text{Pep}} = P_{\text{PP}} = \frac{\gamma Q_{\text{P}} Q_{\text{PP}}}{d_{\text{PP}}^2} \quad (3)$$

$$P_{\text{AimR} \rightarrow \text{Pep}} = P_{\text{RPP}} = \frac{\alpha Q_{\text{R}} Q_{\text{PP}}}{d_{\text{RPP}}^2}, \quad (4)$$

with  $Q_{\text{R}}$  and  $Q_{\text{P}}$  the charges of AimR and AimP genes, respectively. Indeed,  $Q_{\text{X}}$  and  $Q_{\text{PP}}$  charges of AimX gen and peptides, respectively. In this manner Eq. 1 denotes the probability for a decision for lysis.

$$P_{\text{B}} = \frac{\frac{\beta Q_{\text{R}} Q_{\text{X}}}{d_{\text{RX}}^2} \otimes \frac{\gamma Q_{\text{P}} Q_{\text{PP}}}{d_{\text{PP}}^2}}{\frac{\beta Q_{\text{R}} Q_{\text{X}}}{d_{\text{RX}}^2} \otimes \frac{\gamma Q_{\text{P}} Q_{\text{PP}}}{d_{\text{PP}}^2} + \left(1 - \frac{\beta Q_{\text{R}} Q_{\text{X}}}{d_{\text{RX}}^2} \otimes \frac{\gamma Q_{\text{P}} Q_{\text{PP}}}{d_{\text{PP}}^2}\right) \otimes \frac{\alpha Q_{\text{R}} Q_{\text{PP}}}{d_{\text{RPP}}^2}} \quad (5)$$

### 3.1 Approximations

In order to get an idea about the purpose to employ the Coulomb's approach, some approximations can be assumed. For example that all charges have same value. Thus, Eq. 5 reads:

$$P_B = \frac{\frac{\beta\gamma Q^4}{d_{RX}^2}}{\left(\frac{\alpha Q^2}{d_{RPP}^2} + \frac{\beta\gamma Q^4}{d_{RX}^2} - \frac{\beta\gamma\alpha Q^6}{d_{RX}^2 d_{RPP}^2}\right)}. \quad (6)$$

Interestingly at the denominator one can see a polynomial at  $Q$ . It actually can be seen as favorable to the applied methodology of approximation. When the quadratic and quarter terms are of importance, then Eq. 6 has the following form:

$$P_B = \frac{\frac{\beta\gamma Q^4}{d_{RX}^2}}{\left[\frac{\alpha}{d_{RPP}^2} \left(Q^2 + \frac{\beta\gamma d_{RPP}^2 Q^4}{\alpha d_{RX}^2}\right) - \frac{\beta\gamma\alpha Q^6}{d_{RX}^2 d_{RPP}^2}\right]}. \quad (7)$$

Thus with the scale:

$$\frac{\beta\gamma d_{RPP}^2}{\alpha d_{RX}^2} = 1/2! \quad (8)$$

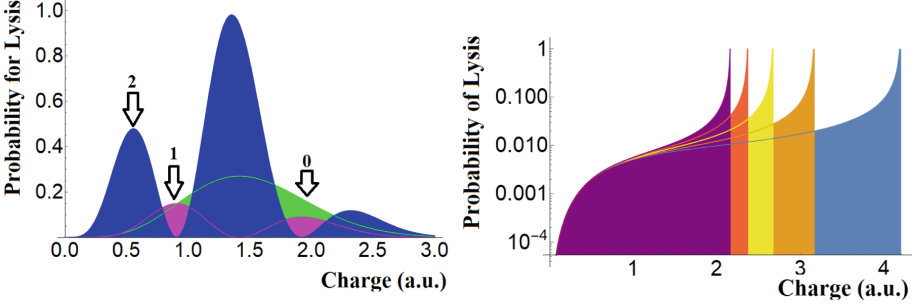
then one can see that an exponential function exists there in the form as:  $Q^2 + 1/2!Q^4 + 1/3!Q^6 + \dots \approx \text{Exp}Q^2$ . An additional assumption is that of  $Q^{2\ell} \approx 0$  if  $\ell \geq 3$ . With this one can arrive to:

$$P_B = \frac{\frac{\beta\gamma Q^4}{d_{RX}^2}}{\left[\frac{\alpha}{d_{RPP}^2} (\text{Exp}Q^2)\right]} = \frac{\beta\gamma Q^4 d_{RPP}^2}{\alpha d_{RX}^2} \text{Exp}(-Q^2). \quad (9)$$

With Eq. 8 the scale allows to write a Weibull-like function for the Bayes's probability that reads:

$$P_B = \frac{Q^4}{2!} \text{Exp}(-Q^2). \quad (10)$$

In this way, Eq. 10 represents the probability to decide on lysis. A point of interest turns out to be the derivatives of  $P_B$ . In Fig. 2 (left panel) the case of Eq. 10 (labeled by 0), and its first (labeled by 1) as well as second derivative (labeled by 2) are shown. The first and second have plotted as their square to put away the negative values. A tentative generalization of Eq. 10 can be written as:  $P_B = \frac{Q^{2m}}{2!} \text{Exp}(-Q^m)$  with  $m \geq 2$ . In virtue of distributions of Fig. 2 and the factor  $1/2!$ , the one can define the probability for decision on lysis is a  $n$ -th derivative of Bayes's probability is given by  $P_{B,n}^{SY} = 0.5 \frac{d^n}{dQ^n} (Q^{2m} \text{Exp}(-Q^m))$ .



**Fig. 2.** Left-side: Plotting of Eq. 10 (green color) with first (magenta color) and second derivative (blue color). Right-side: Probability to execute lysis as function of electric charge. A polynomials  $10^{-2}Q^4/(Q^2 + Q^4 - (0.01 + j * 0.05)Q^6)$  was used for this illustration (details see text below). (Color figure online)

On the other hand one can also determine in a logic way the probability for lysogeny is given for a similar expression =  $P_{B,k}^{SG} = 0.5 \frac{d^k}{dQ^k} (Q^{2m} \text{Exp}(-Q^m))$  for the  $k$ -th derivative of Bayes's probability. Therefore the total probability of "indecision" is written in a straightforward manner as:

$$0.5 \frac{d^n}{dQ^n} [Q^{2m} \text{Exp}(-Q^m)] + 0.5 \frac{d^k}{dQ^k} [Q^{2m} \text{Exp}(-Q^m)] = 1. \quad (11)$$

A compact form for writing Eq. 11 is then given by:

$$0.5 \frac{d^h}{dQ^h} [\delta_{n,h} Q^{2m} \text{Exp}(-Q^m) + \delta_{k,h} Q^{2m} \text{Exp}(-Q^m)] = 1, \quad (12)$$

where  $\delta_{n,h}$  and  $\delta_{k,h}$  the Dirac-delta functions whose purpose here is the factorization of the generalized derivative  $\frac{d^h}{dQ^h}$ . In Fig. 2 (right panel) Eq. 6 was illustrated as:  $10^{-2}Q^4/(Q^2 + Q^4 - (0.01 + j * 0.05)Q^6)$  up to for 5 values of  $j$  (red  $j=1$ , green  $j=2$ , yellow  $j=3$ , red  $j=4$  and purple  $j=5$ ). It is noted that two well-defined phases are seen. When charges acquire their high values, the probabilities for all cases are reaching to 1. It might be the case that AimX is blocked out and to guarantee lysis, AimP releases large volumes of peptides.

## 4 The Cost for Indecisions

The factor 1/2 in Eq. 12 defined as a kind of scale (see Eq. 8) to balance the physical units because the Coulomb's force has been introduced as part of probabilistic model can also be generalized in conjunction of derivatives. It is actually seen in Fig. 2 by which the peaks of distributions are changing with the order of derivative. When not any decision is executed then one expects that the factors 1/2 might be falling down without any chance to back to the initial values.

Therefore one can write a general expression involving different values for such scale. It reads:

$$\xi_1 \frac{d^n}{dQ^n} (Q^{2m} \text{Exp}(-Q^m)) + \xi_2 \frac{d^k}{dQ^k} (Q^{2m} \text{Exp}(-Q^m)) = 1. \quad (13)$$

Unfortunately for phages the cost for indecision is the apparition of subprocesses that might be different away from lysis and lysogeny. It implies that emerges more probabilistic events. Mathematically speaking one has below that:

$$\sum_{\ell}^L \xi_{\ell} \frac{d^{\ell}}{dQ^{\ell}} (\omega^2 Q^{2m} \text{Exp}(-Q^m)) = 1. \quad (14)$$

with  $\xi_{\ell}$  a probability of event including lysis and lysogeny, ranging between 0 and 1, where  $\omega$  is a constant related to charge  $Q$ . Again one can generalize this in the sense that  $\omega^2 Q^{2m}$  is part of a infinite sum:  $\omega Q^m + \omega^2 Q^{2m} + \omega^3 Q^{3m} + \dots$ . Thus one gets:

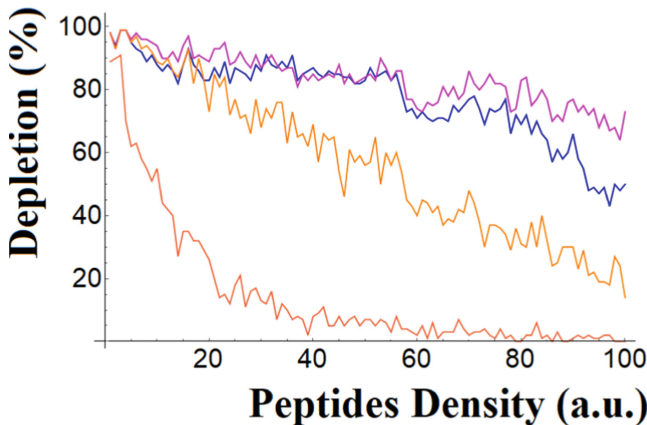
$$\sum_{\ell}^L \xi_{\ell} \frac{d^{\ell}}{dQ^{\ell}} ([\text{Exp}(\omega Q^m)] \text{Exp}(-Q^m)) = \sum_{\ell}^L \xi_{\ell} \frac{d^{\ell}}{dQ^{\ell}} \text{Exp}[Q^m(\omega - 1)] = 1. \quad (15)$$

One can see that when  $L \gg 1$  then both lysis as lysogeny might be strongly affected and not any action is going to be taken. This can happen in events where AimP cannot segregate peptides neither the extracellular conditions appear to be favorable for the propagation of them. Another possibility is the clogging of peptides to go out from the hijacked bacteria. Another fact is the possible interference among the events inside bacteria. It is remarked this since virus might not be so efficient to manage various actions, and instead opt by the ones that can guarantee the fast replication without the necessity to destroy its hostage. For example when AimR activates AimX to inhibit lysogeny, the action that AimP releases peptides through the extracellular zone might origin some interference towards the activation of AimX. Thus emerges the question: Can peptides also to be able to activate AimX. This might to confirm that if  $\xi_{\ell}$  does not belong to either lysis or lysogeny then one can speak about the possible existence of latency state by which not any decision due to interference has been taken.

## 5 Monte Carlo Simulation

So far, it is clear that the role of released peptides is twofold, in one hand they are ejected from AimP in a lysis event, and on the other hand they are binded to AimR to deactivate AimX so that lysogeny is executed. These events can be part of a computational code as presented at the end of this paper. In fact, a main loop runs over a sample of phages that are adhered to bacteria. Thus the

Coulomb's force is used. The probability that AimR activates the inhibitor AimX is estimated and actually it is dependent on the normalization constant  $\beta$ . Actually here it should be noted that the total charge would come from an operation of integration on the charge density. In other words:  $Q = \int \rho(s)dV$ . Aside one can realize that the solving of density would be dictated by the diffusion equation in the sense that peptides are under extracellular propagation in both when (i) are released by AimP and (ii) shall be bonded by AimR. In fact  $d\rho/dt = D\nabla^2\rho$  can be solve in a model 1D by assuming that the virus and bacteria can move in a 2D space. In radial symmetry the Bessel functions constitute an interesting solution. Also, from an initial amount of bacteria, the decisions for lysis or lysogeny are in function of charge density of peptides. In Fig. 3 up to 4 cases de charge density have been plotted. Here the percent of depleted bacteria is done as function the density of peptides in the extracellular case. The Monte Carlo [12] has been built with the Metropolis algorithm: accept or rejection. Thus once the peptide density has been solved then it is normalized. In conjunction to this the volume of bacteria has been estimated in according to peptide density [13]. The questions: (i) Is the normalized volume of peptides greater than a random number, then accept the depletion for fractions. The code that has been built takes a percent per each time that the acceptation or rejection is formulated. The results in Fig. 3 reveals that randomness might be behind the releasing and uptake of peptides. This stochastic view of Arbitrium is dependent on electric charge of genes.



**Fig. 3.** Results of Monte Carlo simulation showing the percent of depletion as function of peptides density. At abundance of peptides the depleted population of bacteria does not follow a linear relation. This simulation that randomness is a key element in Arbitrium.

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**PSEUDO CODE TO ESTIMATE PHAGE DECISION**


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1   DO N =1,NTOT
2   PRX =  $\frac{\beta q_R q_X}{d^2}$  (activates inhibidor)
3   CALL random(rnd1)
4   IF PRX > rnd1 (decision on lysis)
5     lx = lx + 1
6   IF N=NMIN THEN
7     lyx = lx
8   ENDIF
9   ENDF
10  PRPP =  $\frac{\gamma q_P q_R}{d_{PP}^2}$  (untake peptides)
11  CALL random(rnd2)
12  IF PRPP > rnd2 (decision on lysogeny)
13    lg = lg + 1
14  IF N=NMAX THEN
15    lyg = lg
16  ENDIF
17  ENDF
18  IF N=NTOT THEN
19    x1 = lyx/TOT
20    x2 = lyg/TOT
21    IF x1 + x2 < 0.90 THEN
22      Print  $\frac{\text{Log}(\beta \otimes \gamma)}{\text{rnd1} \otimes \text{rnd2}}$ 
23    ENDIF
24  ENDIF
25  END

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## 6 Conclusion

The phenomenon of Arbitrium discovered by Rotem Sorek at 2017 has been simulated with the Monte Carlo technology. To accomplish this a theory based at the Bayes theorem has been developed. The construction of this theory has demanded to assign some physical roles to the genes interaction as well as to the releasing and uptake of peptides. Thus, the states of lysis and lysogeny might not be the only ones, but also more gene-based events also exist and have a probability, fact that minimizes the priority for phages to carry out Arbitrium. The physics has been modeled by the Coulomb-like forces that allows attraction and repulsion in fully concordance to the discovery of Rotem Sorek. Finally the algorithm Monte Carlo has been designed under the view that bacteria population exhibits depletion in response to phages through a decision as to lysis or lysogeny. Thus, the probability of Bayes has been directly compared to random numbers. Simulated distributions are presenting a decreasing at the percent of bacteria population when the peptides density increases, thus phage requires of a large density of these amino acids to accomplish the annihilation of bacteria after their hijacked without negotiation. In future work, a 3D simulation shall be done.

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