

# **Viral System algorithm: foundations and comparison between selective and massive infections**

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**Abstract.-** This paper presents a guided and deep introduction to Viral Systems (VS), a novel bio-inspired methodology based on a natural biological process taking part when the organism has to give a response to an external infection. VS has proven to be very efficient when dealing with problems of high complexity. The paper discusses on the foundations of viral systems, presents the main pseudocodes that need to be implemented and illustrates the methodology application. A comparison between VS and other metaheuristics, as well between different VS approaches is presented. Finally trends and new research opportunities are presented for this bio-inspired methodology.

**Keywords-** Viral System, bio-inspired methodology, optimization, metaheuristic

## **1. Introduction**

Viral Systems is a new bio-inspired methodology simulating the natural biological process taking part when the organism has to give a response to an

external infection. Natural Immune System protects the organism from dangerous external agents such as viruses or bacteria. In this context, antibodies try to protect the organism from such pathogens. Immune systems have a lot of peculiarities that make them very attractive for computational optimization (Cutello et al., 2007a and Cutello et al, 2007b). In certain manner, Viral System (VS) makes use of the same infection-antigenic response concept from immune systems, but from the perspective of the pathogen. That is, the virus infection expansion corresponds to the feasibility region exploration, and the optimum corresponds to the organism lowest fitness value.

Real optimization problems are complex, especially those that are classified as NP-Hard. For such type of problems, available algorithms usually present weaknesses and exact mathematical methods cannot guarantee the optimum of the problem in a bounded time. So, several generalized metaheuristics (as genetic algorithms, tabu search or simulated annealing among others) have successfully tried to deal with such problems. Since the last decade, new research is being undertaken in order to find other natural-life inspired methods to solve this kind of problems. Examples of that are artificial life algorithms, in particular predator prey type models, which are relatively closed to our VS. Van Dyke Parunak (1997) presents a detailed description of such models in a multi-agent system context.

The concept of viruses' analogies has been mainly used as part of genetic algorithms. For instance, Kubota *et al.* (1996) propose them as part of a specific operator in genetic algorithms, and Saito (2003) has described the use of genetic algorithms which make use of a virus evolutionary theory (GAV), and an algorithm based on the conception of horizontal evolution caused by virus

infections. GAV is carried out by attacking a chromosome by a number of viruses, and having the genes of the chromosome recombined by the attack. The infection is allowed when the evaluation value goes up, but it falls into local minima easily. In order to escape from these local minima, an infection which makes the evaluation value worse in a small rate under small probability is allowed as well. All these approaches do not fit with our definition of Viral System as a new metaheuristic what we detail in this paper.

By now, applications of VS application has mainly tested in network problems (Cortés et al, 2008 and Cortés et al, 2010). However, its application to other context can be easily moved as this paper stands.

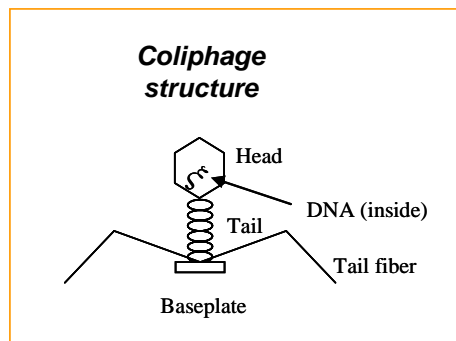
The rest of the paper follows with the presentation of the foundations of Viral Systems in section two. Next, section three details the pseudocode for the two types of considered infections. Section four includes a brief comparison between the detailed two types of infection being presented in this paper. The comparison is made for a well-known network flows problem. The fifth section presents a problem example and illustrates the solution procedure using VS methodology. The final section presents several conclusions and further research opportunities.

## **2. Foundations of Viral Systems**

### **2.1. Viruses, viral infections and organism antigenic response**

Viruses are intracellular parasites shaped by nucleic acids, such as DNA or RNA, and proteins. The protein generates a capsule, called a capsid, where the

nucleic acid is located. The capsid plus the nucleic acid shape the nucleus-capsid, defining the virus. There is a high number of different types of viruses, each of them showing a different and autonomous behaviour. However, the simplest and most common type of virus is the phage, a type of virus infecting bacteria. Figure 1 depicts a traditional representation for such structure.



**Figure 1** Coliphage structure

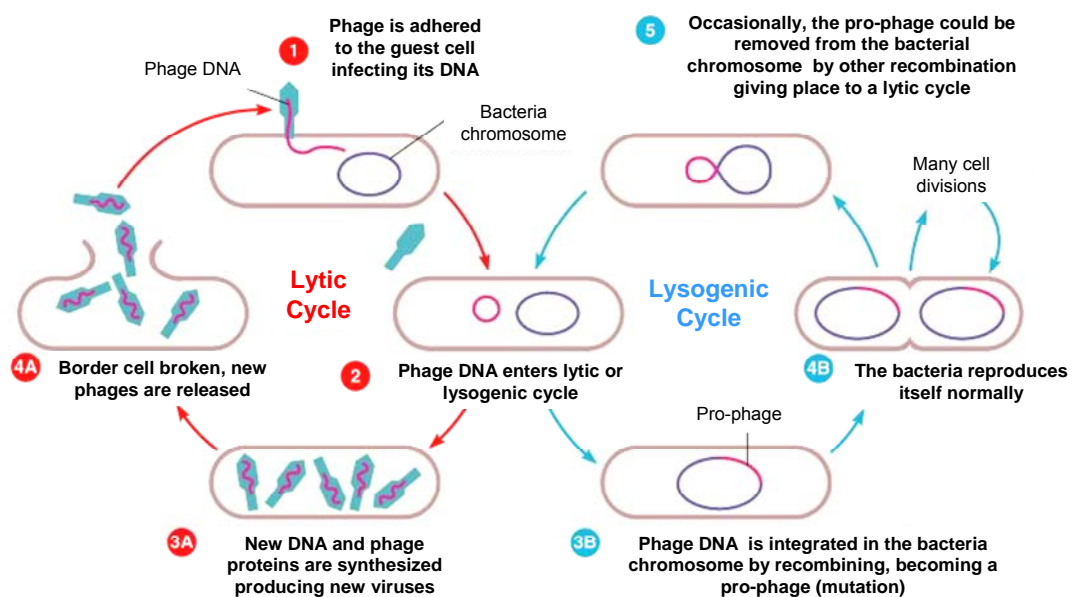
One of the main characteristics of viruses is the replication mechanism. The phage (a common type of virus) does follow lytic replication process. Left side of Figure 2 depicts the biological evolution of the virus infection following the next steps:

1. The virus is adhered to the border of the bacterium. After that, the virus penetrates the border being injected inside this one, (1) and (2) in Figure 2.
2. The infected cell stops the production of its proteins, beginning to produce the phage proteins. So, it starts to replicate copies of the virus nucleus-capsids, (3a) in Figure 2.
3. After replicating a number of nucleus-capsids, the bacterium border is broken, and new viruses are released, (4a), which can infect near cells, (1), in Figure 2.

The life cycle of the virus can be developed in more than one step. Some viruses are capable of lodging in cells giving rise to the lysogenic replication.

This case is shown in the right side of Figure 2. It follows:

1. The virus infects the host cell, being lodged in its genome, (3b) in Figure 2 where a pro-phage (mutation) can arise.
2. The virus remains hidden inside the cell during a while until it is activated by any cause, for example ultraviolet irradiation or X-rays, (i) in Figure 2. During such time the cell reproduces itself normally.
3. The replication of cells altered, with proteins from the virus, starts. So, lysogenic replication produces the genome alteration of the cell leading to a procedure similar to a mutation process.



**Figure 2** Lytic (left) and lysogenic (right) replication of viruses

However, some viruses have the property of leading an antigenic response in the infected organism. In these situations an immune response is originated causing the creation of antibodies. This is the specific case of phages.

So VS follows an exploration process that combines lytic replication to search the neighbourhood of the existing solutions (which is one of the main features of Tabu Search) and a mutation process (which is a characteristic of Genetic Algorithms).

## 2.2. Computational description of Viral Systems

VS is an iterative method that runs during a maximum number of iterations, or until the optimum is reached in case of a known optimum.

VS defines the clinical picture of an infected population as the description of all the cells infected by viruses. Computationally, it includes the encoding of the solution that is being explored (the genome of the cell that is infected, in biological terms) and the number of nucleus-capsids being replicated, NR, (for lytic replications) or the number of hidden generations, IT, (for lysogenic replications). Thus the state of each virus is given by the three-tuple “cell genome-NR-IT”. All these three-tuples corresponding to the cells infected by viruses define the clinical picture.

Every cell infected by a virus develops a lytic or a lysogenic replication according to a probability  $p_{lt}$  (for lytic replication) or  $p_{lg}$  otherwise, where  $p_{lt} + p_{lg} = 1$ .

In case of lysogenic replications, the activation of the mutation process takes place after a limit of iterations has passed (LIT). The value of LIT depends on the cell's health conditions, so a healthy cell (high value of the objective function being minimised,  $f(x)$ ) will have a low infection probability, i.e. the value of LIT will be higher. An unhealthy cell, on the contrary, will have a lower value of LIT.

In case of lytic replications, a number of virus replications (NR) is calculated for each iteration as a function of a binomial variable,  $Z$ , adding its value to the current NR in the clinical picture.  $Z$  is calculated using a Binomial distribution given by the maximum level of nucleus-capsids replicated, LNR, and the single probability of one replication,  $p_r$ :  $Z = \text{Bin}(\text{LNR}, p_r)$ . LNR represents the limit to break the cell border and to release the lodged viruses. As in the lysogenic cycle, the value of LNR is set depending on the value of the objective function being minimised,  $f(x)$ . Thus cells with higher  $f(x)$  have lower probability of getting infected, and therefore the value of LNR will be higher.

Two infections process have been defined for VS: massive infections where a devastating infection reaches a high number of cells, and selective infection where a parsimonious infection following a like-elitist process takes place. An example of the first case is the Ebola virus with a rapid and massive infection that very often produces the death of the patient in a few days, and an example of the second one is the HIV virus, which through a step-by-step evolution destroys the immune system during a process that can take years.

### *2.2.1. Massive infection*

Once a massive infection takes place and viruses are liberated inside the organism, each liberated virus will have a probability,  $p_i$ , of infecting other new cells of the neighbourhood. If the neighbourhood cardinality of  $x$  is defined as  $|V(x)|$ , the number of cells infected by the virus in the neighbourhood can be calculated as a binomial distribution given by  $Y = \text{Bin}(|V(x)|, p_i)$ .

On the other hand, in order to defend itself from the growth of the viral infection, the Organism (the set of cells) responds by releasing antigens. In the clinical

picture, each one of the infected cells generates antibodies according to a Bernoulli probability distribution  $A(x) = \text{Ber}(p_{an})$ , where  $p_{an}$  is the unitary probability of generating antibodies by the cell  $x$  in the clinical picture. Hence, the total population of infected cells generating antibodies is characterized by a Binomial distribution of parameters: the size of the clinical picture,  $n$ , and the probability of generating antibodies,  $p_{an}$ :  $A(\text{population}) = \text{Bin}(n, p_{an})$ .

Also, the antigenic response for every cell in the neighbourhood of an active virus is estimated as a Bernoulli probability distribution given by the probability of generating antibodies,  $p_{an}$ :  $A(x') = \text{Ber}(p_{an}) : x' \in V(x)$ . Therefore, the total number of cells with antibodies in the neighbourhood will follow a Binomial probability distribution given by the total size of the neighbourhood for all the active viruses,  $|V(x)|$ , and the probability of generating antibodies,  $p_{an}$ :  $A = \text{Bin}(|V(x)|, p_{an})$ .

In this situation, a Markovian Process defines the evolution of the clinical picture (Cortés *et al.* 2008). Let  $\pi = (\pi_0, \pi_1, \dots, \pi_{\text{LNR}})$  be the probability of a cell with 0, 1, ..., LNR nucleus-capsids replicated. Equations (1-3) are satisfied in steady state.

$$\pi = \pi \cdot P \quad (1)$$

$$\pi_j = \frac{1}{1 - p_0} \left( \sum_{k=0}^{j-1} p_{j-k} \cdot \pi_k \right) \quad \forall j = 1, 2, \dots, \text{LNR} \quad (2)$$

$$\pi_0 + \pi_1 + \dots + \pi_{\text{LNR}} = 1 \quad (3)$$

To ensure computational control of the infection evolution, we can give (4) as an adequate value for  $p_{an}$ .

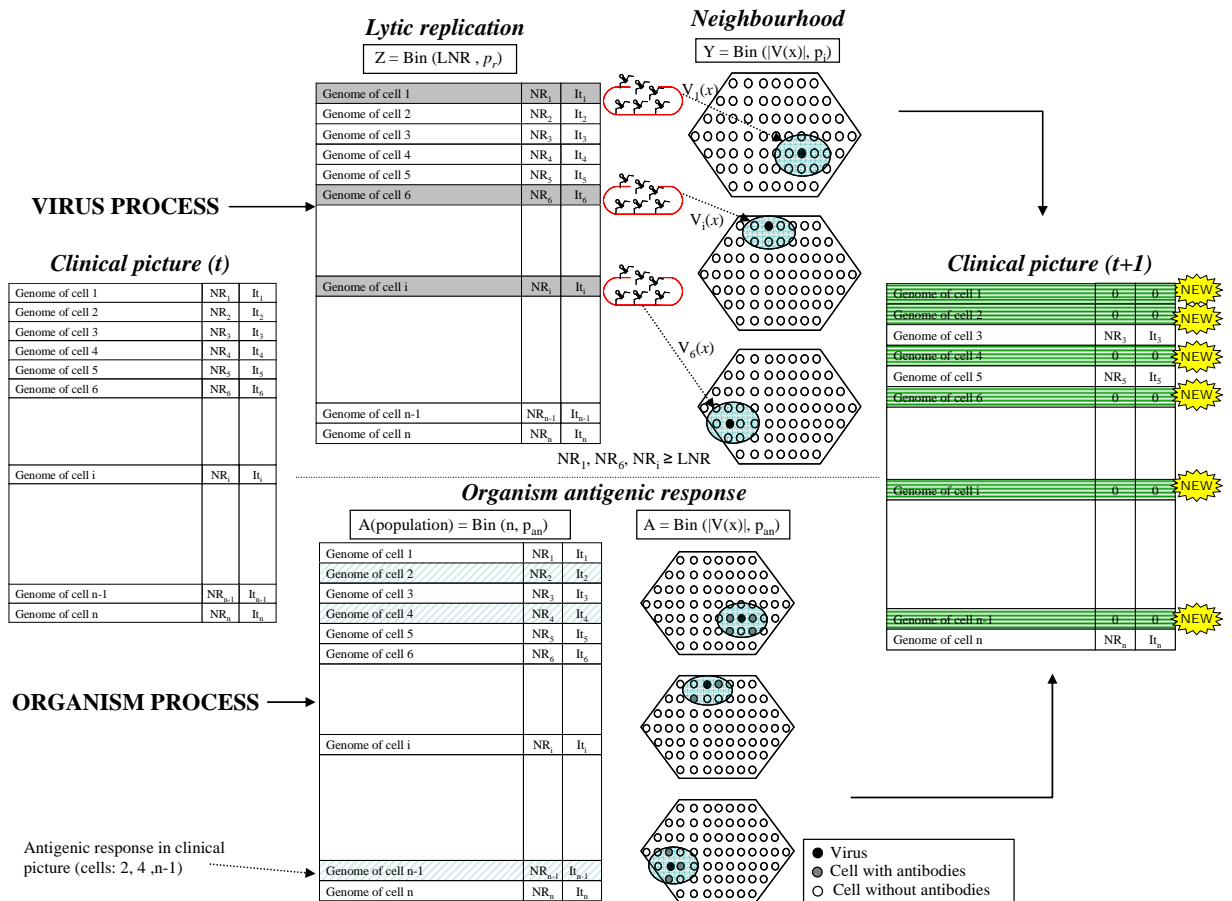


$$p_{an} > \frac{n \cdot \pi_{LNR} \cdot (p_i \cdot |\overline{V(x)}| - 1)}{n \cdot \pi_{LNR} \cdot (p_i \cdot |\overline{V(x)}| - 1) + n} \quad (4)$$

Where  $|\overline{V(x)}|$  is the average neighbourhood size for a specific problem.

However, we do not use the same value of  $p_{an}$  for all the cells. In fact, a higher value of  $f(x)$  implies a healthy cell and therefore this cell will have a higher probability of developing an antigenic response. On the contrary, a cell with a low value of  $f(x)$  represents an unhealthy cell with a lower probability of developing an antigenic response. Thus we define for each cell its specific  $p_{an}(x)$ . To deal with it in computational terms, we use a hypergeometric function, where the cell with an inverse objective function evaluation,  $\frac{1}{f(x)}$ , in ranking position- $i$ , has a probability of generating antibodies,  $p_{an}(x)$ , that is given by  $q(1-q)^i$ , with  $q$  equal to the probability of generating antibodies for the worst individual. Finally, a residual probability remains, which is added to the worst individual.

Figure 3 describes the algorithmic process. The original state is depicted by the clinical picture on the left-hand side. The viruses reaching the level of nucleus-capsids (LNR) break the border and start infecting new cells in their neighbourhoods. The response of the Organism is characterized by the antigenic response, liberating space in the clinical picture, and by creating antibodies in cells located in the virus neighbourhood. This situation leads to a new clinical picture, depicted on the right-hand side of the figure, with new infected cells lodging viruses.



**Figure 3** Algorithmic for lytic replication case in massive infections

### 2.2.2. Selective infection

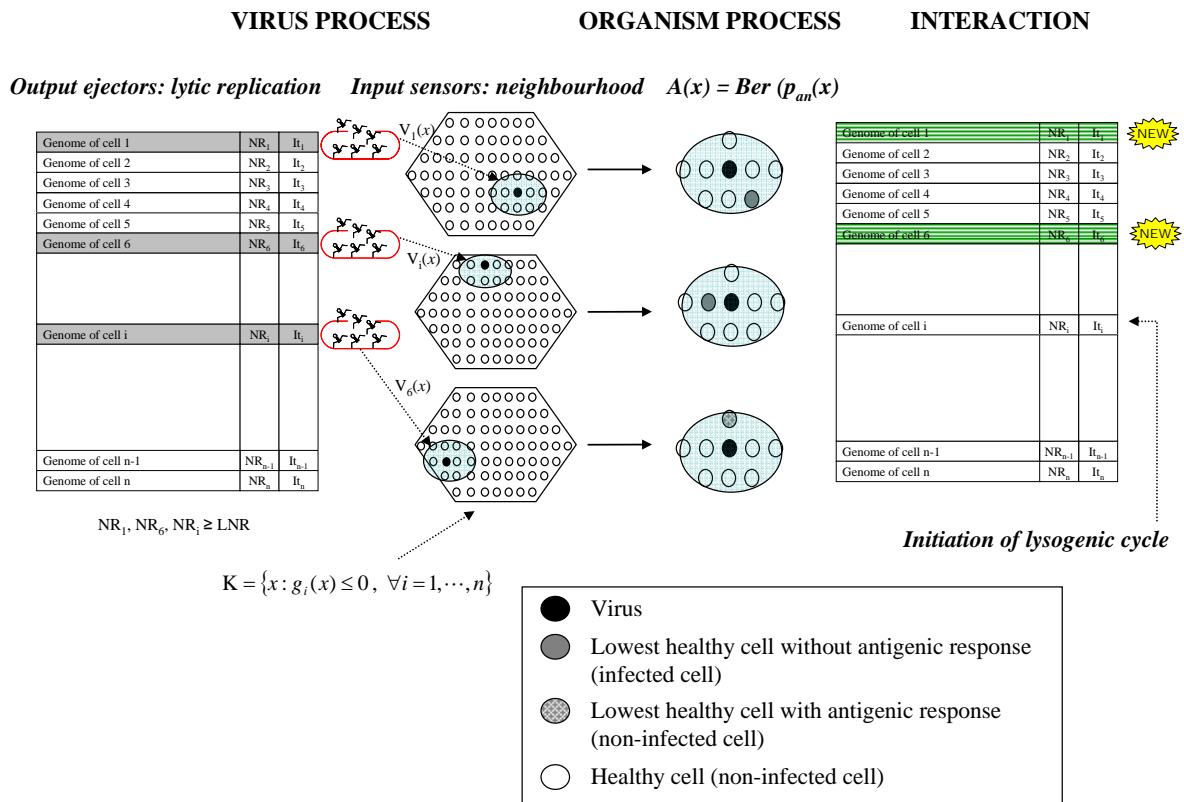
Once a selective infection takes place and viruses are liberated inside the organism, the virus selects a cell with a low value of  $f(x)$  in the neighbourhood. However, the virus will not be able to infect those cells that have developed antigens.

Higher values of  $f(x)$  imply healthy cells and therefore cells that have a higher probability of developing antigenic responses. On the contrary, cells with low value of  $f(x)$  imply unhealthy cells with lower probability of developing antigenic responses. This effect is represented by the previously introduced hypergeometric function.

Then, if the probability of generating antibodies for the case of cell  $x$  is  $p_{an}(x)$ ,  $A(x)$  is defined as a Bernoulli random variable:  $A(x) = \text{Ber}(p_{an}(x))$ .

If cell  $x$  generates antibodies, the cell is not infected and it is therefore not included in the new clinical picture. For recording this clinical picture we use the original cell (that was infected by the virus and that reached the LNR limit) and we initiate a lysogenic cycle for that cell.

Figure 4 defines the algorithm evolution for the infection. The initial state is on the left-hand side: the virus process starts with viruses breaking the border and starting the infection of new cells in their neighbourhoods. Each virus selects the most promising cell, which is the least healthy cell. The Organism process is characterized by the probability of antigenic response in the least healthy cell. Those cells developing antibodies are not infected. Finally, the interaction (right hand side of the figure) defines the new clinical picture, with new infected cells lodging viruses. The cells generating antibodies follow a new lysogenic replication.



**Figure 4** Algorithm for lytic replication case in selective infection

### 3. VS pseudocodes

#### 3.1. VS selective infection pseudocode

Table 1 describes the main functions to be considered for a selective infection. The general pseudocode functions and procedures need to be complemented with each specific problem procedures. These are mainly the neighbourhood characterization and the problem-oriented lysogenic replication.

**Table 1** General pseudocode for VS selective infection

```

procedure Virus_System( $N_{max}$ , Clinical_Size,  $p_{lt}$ ,  $p_i$ ,  $p_{an}$ ,  $p_r$ , LNR, LIT)
   $CP = \emptyset$  /* Clinical Picture
  /* Get Initial Clinical Picture
  for  $i = 1$  to Clinical_Size
    /* Get randomly a feasible solution and assign randomly a replication type
     $CP(i) = \text{Get\_Random\_Feasible\_Solution}()$ 
     $CP(i).\text{Replicat\_Type} = \text{Get\_Random\_Replication\_Type}(p_{lt})$ 
  next
  do
     $iterations = iterations + 1$ 
     $i = \text{Select\_Random\_Solution}(Clinical\_Size)$ 
    if  $CP(i).\text{Replicat\_Type} = \text{'Lytic'}$  Then  $\text{Lytic\_Replication}(CP(i), p_{lt}, p_i, p_{an}, p_r, LNR)$ 
    else  $\text{Lysogenic\_Replication}(CP(i), p_{lt})$ 
  loop until  $iterations = N_{max}$  or  $\text{Check\_Gap}(CP) = \text{True}$ 
end Virus_System
-----
procedure Lytic_Replication ( $C_S$ ,  $p_{lt}$ ,  $p_i$ ,  $p_{an}$ ,  $p_r$ , LNR)
 $C_S = \text{Current solution}$ 
/* Get the number of replicated nucleus-capsids
 $z = \text{Get\_Random\_Binomial\_Probability}(LNR, p_r)$ 
do
   $i = i + 1$ 
  if  $z < \text{Binomial}(i)$  then  $P(c).NR = P(c).NR + 1$ 
loop until  $i = LNR$  or  $z \geq \text{Binomial}(i)$ 
/* Check infection
if  $C_S.NR > C_S.LNR$  then
  /* Get the list  $V_S$  of neighbouring solutions of  $C_S$  in descending order
  regarding solution health
   $VA_S = \text{Get\_Arranged\_Neighbourhood}(V_S)$ 
  /* Get the clinical picture  $CP$  in ascending order regarding solution health
   $CP_A = \text{Get\_Arranged\_Clinical\_Picture}(CP)$ 
   $i = 1$ 
  for each  $S' \in VA_S$ 
    if  $i \leq |CP_A|$  then
       $replace = \text{false}$ 
      do
         $a = \text{Get\_Random\_Binomial\_Probability}(|V_S|, p_{an})$ 
         $b = \text{Get\_Random\_Binomial\_Probability}(|V_S|, p_i)$ 
        if  $a > p_{an}$  and  $b > p_i$  then /* Replace  $CP_A(i)$  with a new solution  $C_{S'}$ 
           $CP_A(i) = C_{S'}$ 
           $CP_A(i).\text{Replicat\_Type} = \text{Get\_Random\_Replicat\_Type}(p_{lt})$ 
           $replace = \text{true}$ 
         $i = i + 1$ 
      loop until  $replace = \text{true}$  or  $i > |CP_A|$ 
    end-for
end Lytic_Replication
-----
procedure Lysogenic_replication( $C_S$ ,  $p_{lt}$ )
 $C_S.IT = C_S.IT + 1$ 
if  $C_S.IT > C_S.LIT$  then
   $s = \text{Get\_Random\_Gen}()$ 
  /* apply move of mutation on  $C_S$ 
   $C_S^{NEW} = \text{Mutation}(C_S, s)$ 
   $C_S^{NEW}.\text{Replicat\_Type} = \text{Get\_Random\_Replication\_Type}(p_{lt})$ 
return  $C_S$ 
end Lysogenic_replication

```

### 3.2. VS massive infection pseudocode

The main difference between massive and selective infection processes is the infection activity every time the algorithm makes iteration. In the selective infection case, only a single cell is infected whereas in the massive one, all cells are infected at each iteration. However, lytic and lysogenic replications are the same for both processes. Therefore, the differences in the pseudocode of the massive process respect to the selective process only appear in the main procedure. Table 2 shows the general procedure for the massive infection process; meanwhile lytic and lysogenic procedures remain as the same procedures showed in Table 1.

**Table 2** General pseudocode for VS massive infection

```
Procedure Virus_System( $N_{max}$  , clinical_size ,  $p_{1t}$  ,  $p_i$  ,  $p_{an}$  , LNR , LIT)
  CP =  $\emptyset$  {Clinical Picture}
  iterations = 0
  Get_Initial_Clinical_Picture(CP , clinical_size ,  $p_{1t}$ )
  Do
    iterations = iterations + 1
    For  $c = 1$  to clinical_size
      If Replicat_Type(CP( $c$ )) = 'Lytic' Then
        Lytic_Replication ( $c$  , LNR)
      Else
        Lysogenic_Replication( $c$ )
      End If
    Next
  Loop Until iterations=  $N_{max}$  or Check_Gap(CP) = True
End Procedure
```

## 4. A brief comparison between VS massive and selective infections

In order to illustrate the performance of VS massive and selective infections and the degree of complementarity between them depending on the specific characteristics of the problem, we bring here a well-known network problem (the

Steiner tree problem) that has been previously dealt with in our previous works (Cortés *et al.* 2008; and Cortés *et al.* 2010).

To test the two approaches, we used the OR-Library that can be accessed in the website <http://people.brunel.ac.uk/~mastjib/jeb/info.html> (Beasley, 2010), considering series SteinC, SteinD and SteinE. We divided the Steiner tree problem into three groups: Group No.1 is a low terminal density group that contains problems with less than 15% of terminal nodes; group No. 2 corresponds to medium terminal density and consists of problems with more than 15% and less than 30% of terminal nodes; and group No. 3 features problems with more than 30% of terminals.

Tables 3, 4 and 5 show the results for each VS approach depending on the terminals' structure.

**Table 3** Comparison on VS massive and selective infections: case low terminal density

Instance	Optimum	Nodes	Terminals	% term	Group	VS-massive	VS-selective
steinc01.txt	85	143	5	3,5%	1	0,00%	0,00%
steinc02.txt	144	128	10	7,8%	1	0,00%	0,00%
steinc06.txt	55	366	5	1,4%	1	0,00%	0,00%
steinc07.txt	102	383	10	2,6%	1	0,00%	0,00%
steinc11.txt	32	499	5	1,0%	1	0,00%	0,00%
steinc12.txt	46	499	10	2,0%	1	0,00%	0,00%
steinc16.txt	11	500	5	1,0%	1	0,00%	0,00%
steinc17.txt	18	500	10	2,0%	1	0,00%	0,00%
steind01.txt	106	272	5	1,8%	1	0,00%	0,00%
steind02.txt	220	283	10	3,5%	1	0,00%	0,00%
steind06.txt	67	759	5	0,7%	1	2,99%	0,00%
steind07.txt	103	749	10	1,3%	1	0,00%	0,00%
steind11.txt	29	993	5	0,5%	1	0,00%	0,00%
steind12.txt	42	1000	10	1,0%	1	0,00%	0,00%
steind16.txt	13	1000	5	0,5%	1	0,00%	0,00%
steind17.txt	23	1000	10	1,0%	1	0,00%	0,00%
steine01.txt	111	678	5	0,7%	1	3,60%	0,00%
steine02.txt	214	710	10	1,4%	1	0,93%	0,00%
steine06.txt	73	1842	5	0,3%	1	31,51%	0,00%
steine07.txt	145	1885	10	0,5%	1	11,03%	0,00%
steine11.txt	34	2498	5	0,2%	1	5,88%	0,00%
steine12.txt	67	2499	10	0,4%	1	7,46%	0,00%
steine16.txt	15	2500	5	0,2%	1	0,00%	0,00%
steine17.txt	25	2500	10	0,4%	1	0,00%	0,00%
Average						2,64%	0,00%
Standard Deviation						6,65%	0,00%
Maximum Error						31,51%	0,00%
No. of optimums						17	24
Best approach						17	24

**Table 4** Comparison on VS massive and selective infections: case medium terminal density

Instance	Optimum	Nodes	Terminals	% term	Group	VS-massive	VS-selective
steinc08.txt	509	387	79	20,4%	2	0,39%	0,00%
steinc09.txt	707	418	124	29,7%	2	0,00%	0,00%
steinc13.txt	258	498	83	16,7%	2	0,00%	0,00%
steinc14.txt	323	499	125	25,1%	2	0,00%	0,00%
steinc18.txt	113	500	83	16,6%	2	0,00%	0,00%
steinc19.txt	146	500	125	25,0%	2	0,00%	0,00%
steind08.txt	1072	802	166	20,7%	2	0,47%	0,47%
steind13.txt	500	998	167	16,7%	2	0,20%	0,00%
steind14.txt	667	998	250	25,1%	2	0,00%	0,15%
steind18.txt	223	1000	167	16,7%	2	0,00%	0,90%
steind19.txt	310	1000	250	25,0%	2	0,00%	0,65%
steine08.txt	2640	1936	409	21,1%	2	1,78%	1,14%
steine13.txt	1280	2495	417	16,7%	2	0,55%	1,33%
steine14.txt	1732	2497	625	25,0%	2	0,29%	0,64%
steine18.txt	564	2500	417	16,7%	2	0,35%	2,66%
steine19.txt	758	2500	625	25,0%	2	0,00%	1,18%
Average						0,25%	0,57%
Standard Deviation						0,44%	0,72%
Maximum Error						1,78%	2,66%
No. of optimums						9	7
Best approach						13	8

**Table 5** Comparison on VS massive and selective infections: case high terminal density

Instance	Optimum	Nodes	Terminals	% term	Group	VS-massive	VS-selective
steinc03.txt	754	178	75	42,1%	3	0,00%	0,00%
steinc04.txt	1079	193	102	52,8%	3	0,00%	0,00%
steinc05.txt	1579	223	180	80,7%	3	0,00%	0,00%
steinc10.txt	1093	427	242	56,7%	3	0,00%	0,00%
steinc15.txt	556	500	250	50,0%	3	0,00%	0,00%
steinc20.txt	267	500	250	50,0%	3	0,00%	0,00%
steind03.txt	1565	350	148	42,3%	3	0,00%	0,00%
steind04.txt	1935	359	207	57,7%	3	0,10%	0,00%
steind05.txt	3250	470	377	80,2%	3	0,03%	0,00%
steind09.txt	1448	802	246	30,7%	3	0,48%	0,69%
steind10.txt	2110	836	485	58,0%	3	0,14%	0,00%
steind15.txt	1116	996	498	50,0%	3	0,00%	0,00%
steind20.txt	537	1000	500	50,0%	3	0,37%	0,37%
steine03.txt	4013	886	364	41,1%	3	0,50%	0,24%
steine04.txt	5101	951	537	56,5%	3	0,33%	0,00%
steine05.txt	8128	1175	938	79,8%	3	0,44%	0,00%
steine09.txt	3604	2002	613	30,6%	3	0,50%	0,47%
steine10.txt	5600	2076	1196	57,6%	3	0,70%	0,14%
steine15.txt	2784	2498	1250	50,0%	3	0,22%	0,00%
steine20.txt	1342	2500	1250	50,0%	3	0,00%	0,15%
Average						0,19%	0,10%
Standard Deviation						0,22%	0,19%
Maximum Error						0,70%	0,69%
No. of optimums						9	14
Best approach						10	18

The analysis of the results remarks the complementarity between both approaches. VS selective infection case proved to be a very efficient approach for a complex NP-Hard problem as the Steiner tree is. However, although VS selective infection case showed a general better behaviour (especially for Tables 3 and 5), VS massive infection case showed a very interesting good behaviour for the most complex case in the Steiner tree problem: the case of a



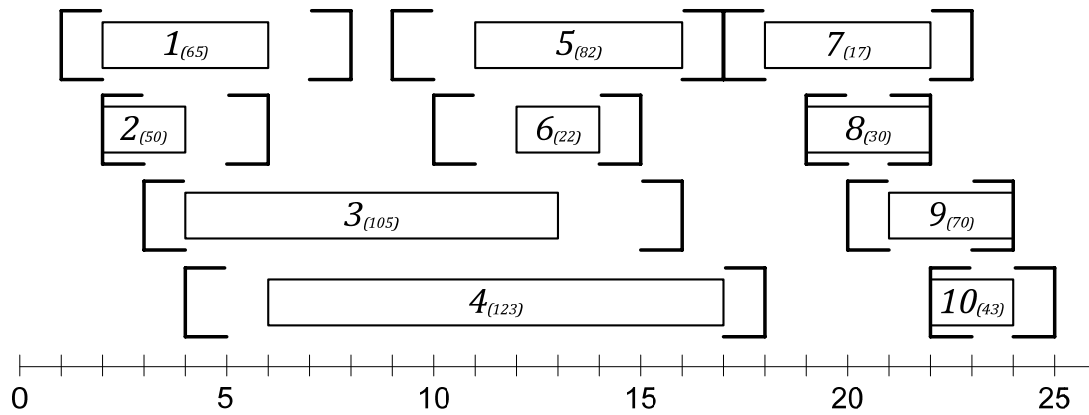
medium density of terminals. Within this range of comparison the massive approach outperformed the selective one. Furthermore, the massive infection approach maintained a bounded distribution of its standard deviation, which provides a better adjustment around the optimum. It also provided the best solution for all the problems except for C8 (0.39% error versus 0.00%), D13 (0.20% versus 0.00%) and E8 (1.78% versus 1.14%).

## **5. Illustration: the Variable job Scheduling Problem (VSP)**

We make use of the variable job scheduling problem to illustrate the VS methodology. Initially, we are representing the virus evolution for a selective infection case.

The Variable job Scheduling Problem (VSP) (see Gertsbakh and Stern, 1978; Gabrel, 1995; and Wolfe and Sorensen, 2000 for relevant references), is characterized as the problem of scheduling, on a set of parallel machines, a number of non-preemptive jobs, each with a time interval for its processing. For a fixed number of machines, the objective is maximizing the weighted number of jobs processed, assuming a weight for each job. VSP is NP-Complete in all of the cases (Kovalyov and Cheng, 2007). On the other hand, it is also possible to consider a tactical objective that calculates the number of machines necessary to process all jobs.

Figure 5 presents an illustration of the problem considering 10 jobs. Between parentheses we represent the weight of the job and the processing time corresponds to the width of each rectangle. Square brackets represent the time windows for the processing. For the problem we have 2 machines.



**Figure 5** Illustration of the VSP

Next we are going to describe an illustration of the lytic and the lysogenic replication. We could consider this illustration included in both, selective and massive infection procedure.

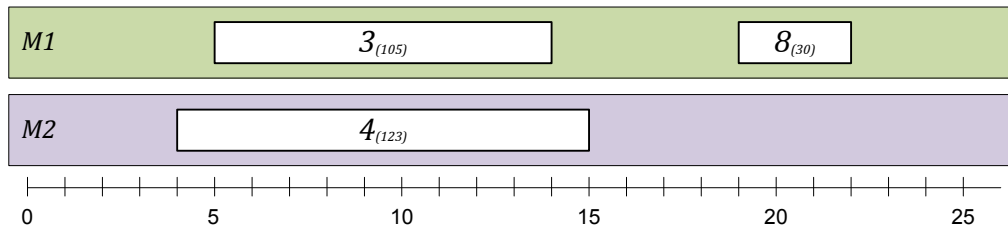
For an iteration  $t$ , we could imagine a population as that showed in Table 6, considering 5 cells. First column shows selected jobs and, between parenthesis, machine that processes the job and its starting time instant. Cells 2, 4 and 5 have a lytic replication whereas for cells 1 and 3 the replication is lysogenic.

**Table 6** Population for the iteration  $t$

jobs (machine, starting time instant)	NR	IT	fitness	LNR	LIT
1(1,2) . 4(2,5) . 7(1,17)	0	IT <sub>1</sub>	205	0	LIT <sub>1</sub>
2(1,3) . 5(1,11) . 6(2,12) . 9(2,20)	NR <sub>2</sub>	0	224	LNR <sub>2</sub>	0
4(1,6) . 5(2,10) . 7(1,18) . 10(2,23)	0	LIT <sub>3</sub>	265	0	LIT <sub>3</sub>
3(1,5) . 4(2,4) . 8(1,19)	LNR <sub>4</sub>	0	258	LNR <sub>4</sub>	0
1(1,2) . 3(1,6) . 6(2,13) . 7(1,17)	NR <sub>5</sub>	0	209	LNR <sub>5</sub>	0

## 5.1. Illustration lytic Replication

If the algorithm randomly selects cell 4 (Figure 6) to be replicated, and NR4 reaches LN4, we can illustrate the lytic process as follows.

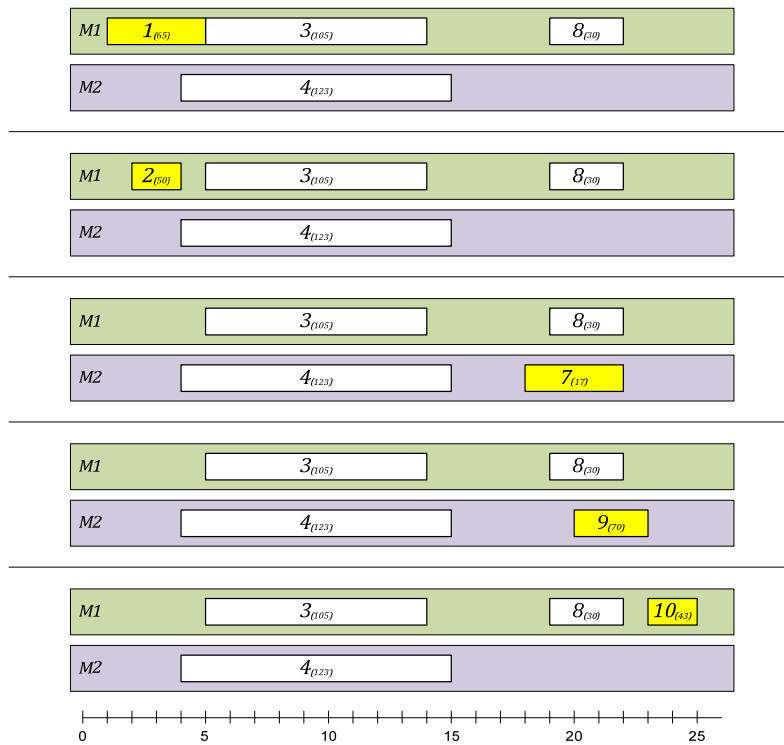


**Figure 6** Cell 4

For simplicity and since we are going to consider a short neighbourhood, we calculate all neighbouring solutions of cell 4. To obtain the neighbourhood, we define three moves: insertion, replacement and displacement.

### 5.1.1. Insertion

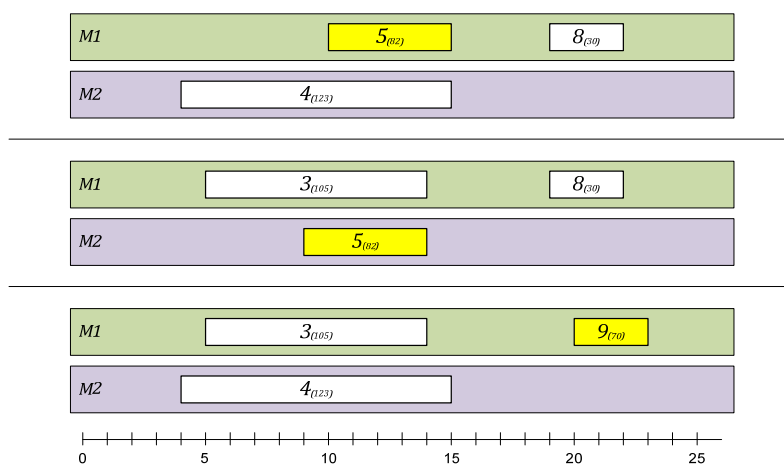
We try to insert jobs that are not in the solution of the cell. Figure 7 shows all possible solutions with an insertion move.



**Figure 7** Insertion moves

### 5.1.2. Replacement

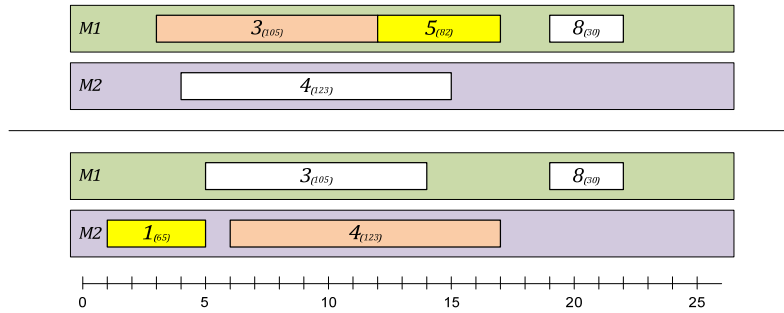
We change each job in the solution for another that is not there. We give more probability to jobs with a greater weight.



**Figure 8** Replacement moves

### 5.1.3. Displacement

The last move inserts jobs through the movement of each job in the solution. As the previous move, if more than one job can be inserted, we discriminate with the weight of the job.



**Figure 9** Displacement moves

After generating the neighbourhood (Figure 10), we arrange the list of neighbouring solutions in descending order regarding solution health (Figure 11).

	jobs (m,k)	NR	IT	fitness	LNR	LIT
Insertion	1(1,1) . 3(1,5) . 4(2,4) . 8(1,19)	0	0	323	0	0
	2(1,2) . 3(1,5) . 4(2,4) . 8(1,19)	0	0	308	0	0
	3(1,5) . 4(2,4) . 7(2,18) . 8(1,19)	0	0	275	0	0
	3(1,5) . 4(2,4) . 8(1,19) . 9(2,20)	0	0	328	0	0
	3(1,5) . 4(2,4) . 8(1,19) . 10(1,23)	0	0	301	0	0
Replacement	4(2,4) . 5(1,10) . 8(1,19)	0	0	235	0	0
	3(1,5) . 5(2,9) . 8(1,19)	0	0	217	0	0
	3(1,5) . 4(2,4) . 9(1,20)	0	0	298	0	0
Displacement	3(1,3) . 4(2,4) . 5(1,12) . 8(1,19)	0	0	340	0	0
	1(2,1) . 3(1,5) . 4(2,6) . 8(1,19)	0	0	323	0	0

**Figure 10** Neighbourhood

jobs (m,k)	NR	IT	fitness	LNR	LIT
3(1,3) . 4(2,4) . 5(1,12) . 8(1,19)	0	0	340	0	0
3(1,5) . 4(2,4) . 8(1,19) . 9(2,20)	0	0	328	0	0
1(1,1) . 3(1,5) . 4(2,4) . 8(1,19)	0	0	323	0	0
1(2,1) . 3(1,5) . 4(2,6) . 8(1,19)	0	0	323	0	0
2(1,2) . 3(1,5) . 4(2,4) . 8(1,19)	0	0	308	0	0
3(1,5) . 4(2,4) . 8(1,19) . 10(1,23)	0	0	301	0	0
3(1,5) . 4(2,4) . 9(1,20)	0	0	298	0	0
3(1,5) . 4(2,4) . 7(2,18) . 8(1,19)	0	0	275	0	0
4(2,4) . 5(1,10) . 8(1,19)	0	0	235	0	0
3(1,5) . 5(2,9) . 8(1,19)	0	0	217	0	0

Figure 11 Neighbourhood

Then, we try to replace the cell replicated with one of those solutions, starting from the best solution. For the illustration, we assume that the method replace the first one, i.e., the best solution.

Jobs (m,k)	NR	IT	fitness	LNR	LIT
1(1,2) . 4(2,5) . 7(1,17)	0	IT <sub>1</sub>	205	0	LIT <sub>1</sub>
2(1,3) . 5(1,11) . 6(2,12) . 9(2,20)	NR <sub>2</sub>	0	224	LNR <sub>2</sub>	0
4(1,6) . 5(2,10) . 7(1,18) . 10(2,23)	0	LIT <sub>3</sub>	265	0	LIT <sub>3</sub>
3(1,5) . 4(2,4) . 8(1,19)	LNR <sub>4</sub>	0	258	LNR <sub>4</sub>	0
1(1,2) . 3(1,6) . 6(2,13) . 7(1,17)	NR <sub>5</sub>	0	209	LNR <sub>5</sub>	0

Jobs (m,k)	NR	IT	fitness	LNR	LIT
1(1,2) . 4(2,5) . 7(1,17)	0	IT <sub>1</sub>	205	0	LIT <sub>1</sub>
2(1,3) . 5(1,11) . 6(2,12) . 9(2,20)	NR <sub>2</sub>	0	224	LNR <sub>2</sub>	0
4(1,6) . 5(2,10) . 7(1,18) . 10(2,23)	0	LIT <sub>3</sub>	265	0	LIT <sub>3</sub>
3(1,3) . 4(2,4) . 5(1,12) . 8(1,19)	0	0	340	LNR <sub>4 (new)</sub>	0
1(1,2) . 3(1,6) . 6(2,13) . 7(1,17)	NR <sub>5</sub>	0	209	LNR <sub>5</sub>	0

Figure 12 New population

Randomly, we choice the new cell type for the cell replicated. LNR value for the cell is calculated as (5):

$$LNR_x = LNR_0 \frac{f(\hat{x}) - f(x)}{f(\hat{x})} \quad (5)$$

where  $\hat{x}$  is the best cell so far,  $x$  is the new cell and  $LNR_0$  is the initial value for LNR.

$LIT_x$  is calculated in a similar way as (6):

$$LIT_x = LIT_0 \frac{f(\hat{x}) - f(x)}{f(\hat{x})} \quad (6)$$

To end the iteration, we check if the new solution generated is the best solution found so far in order to update  $\hat{x}$ .

## 5.2. Illustration lysogenic replication

We suppose that a lysogenic cell is chosen to be replicated in the next iteration: let cell 3 of the population (represented in Figure 13). We also suppose  $LIT_3 = LIT_3$ .

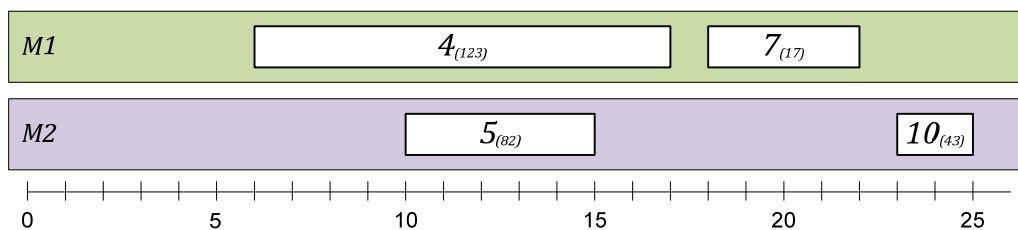
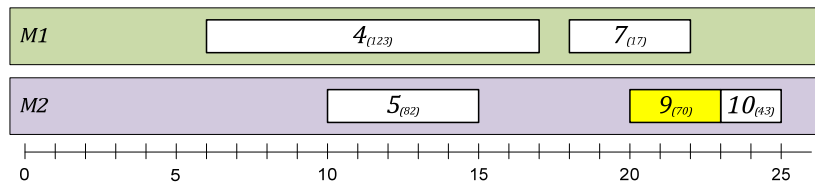


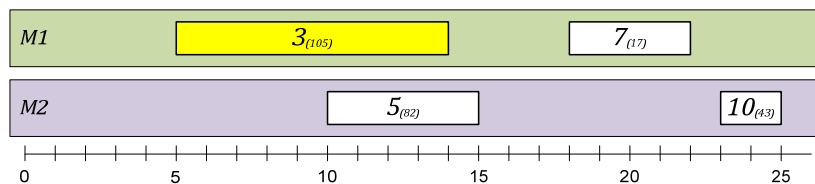
Figure 13 Cell 3

We randomly select a job  $k$ . If job  $k$  is not in the solution, we try to insert job  $k$  in the solution of cell 3. For example, if selected job is 9, we could insert it in machine 2 (Figure 14).



**Figure 14** Lysogenic Insertion

On the other hand, if job  $k$  belongs to the solution, then we try a replacement move with job  $k$ , as in lytic replication. For example, if  $k = 4$ , we can replace job 4 by job 3, as figure 15 shows.



**Figure 15** Lysogenic replacement

If any job can replace job  $k$ , then we get a worse solution than the original, because we extract to the solution job  $k$  in all of the cases.

As in the lytic replication, we randomly assign a replication type for the new cell and calculate its new LIT or LNR.

Finally, we include a brief summary in Table 7 showing results of comparison between selective infection virus and an implementation of a Tabu Search approach that was created with the same definition of neighbourhood used for the lytic replication. The numbers of iterations for VS was 10,000 and 1,000 for



Tabu Search, in order to spend similar processing times. The rest of parameters of the algorithms were previously fixed in a suitable manner after calibration.

**Table 7** Summary of results

Window size	Work Load	Jobs	Selective Virus		Tabu Search	
			Avg. Error (%)	Avg. Time (sec)	Avg. Error (%)	Avge. Time (sec)
[1,5]	Low	25	0,38	4,50	1,60	3,00
[1,5]	Medium	25	0,00	5,40	1,02	1,90
[1,5]	High	25	0,00	5,80	2,46	2,60
[1,10]	Low	25	0,05	6,90	3,91	4,70
[1,10]	Medium	25	0,00	7,10	1,71	4,60
[1,10]	High	25	0,00	8,80	2,39	4,60
[1,5]	Low	50	1,98	5,50	5,39	11,40
[1,5]	Medium	50	0,65	9,60	3,93	14,40
[1,5]	High	50	0,51	11,20	3,40	14,80
[1,10]	Low	50	3,14	8,80	8,10	30,20
[1,10]	Medium	50	1,44	13,20	4,60	37,80
[1,10]	High	50	1,07	17,70	3,86	37,90
[1,5]	Low	100	3,97	31,90	8,67	51,90
[1,5]	Medium	100	3,07	44,60	7,09	83,80
[1,5]	High	100	2,03	62,30	5,77	95,80
[1,10]	Low	100	5,45	46,10	10,68	120,10
[1,10]	Medium	100	4,44	67,80	10,70	217,80
[1,10]	High	100	4,17	100,00	7,71	260,30

Windows size is the starting interval size for each job. They are uniformly and randomly generated in the range [1,5] and [1,10]. Work load express the number of jobs per instant of the time horizon. Low work load represents an 80-90% of jobs processed; medium work load a 50-60%; and high work load a 25-35%.

All instances have been solved by an optimizer, in order to obtain the optimal solution and to be able to test the performance for both methods. Error averages are taken over 10 instances generated for each tuple (Windows Size, Work Load, and number of jobs). Average computational times are provided in

CPU seconds. We used Lingo Optimizer to get optimal solutions and calculate average errors.

Computational results in Table 7 show how the VS selective implementation provides better results for all the cases than Tabu Search. Also, regarding CPU time, Tabu Search presents a worse behavior for, practically, all the instances.

## **6. Conclusions and further research**

VSs have proven successful when dealing with network complex problems. Its extension to other complex problems is promising and new papers dealing with this novel bio-inspired approach should be expected in the scientific literature.

Future research could consider several aspects. First, as VS is still a novel field of research VS could be applied to solve numerous computational complexity problems, several of them well known in the scientific literature and characterized as NP-Hard problems. However, one of the most challenging approaches is to focus on testing new viruses different from phages to explore their optimisation capabilities and particular behaviour. In fact, lytic and lysogenic replication cycles of phagocytes correspond to the less complex virus infection, and it is easy to think that more complex infection forms could lead to more successful infection process. The goal would be the generation of an optimisation library associated to different classes of viruses and capable of adapting to each specific problem. However, this research will require a previous detailed medical investigation to clearly characterize the different viral processes, and multidisciplinary research teams would be very welcome.

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