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A novel application of queueing theory on the Caulerpenyne secreted by invasive *Caulerpa taxifolia* (Vahl) C.Agardh (Ulvophyceae, Caulerpales): a preliminary study

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Abstract

Aquarium originated marine green alga Caulerpa taxifolia was introduced into the Mediterranean Sea accidentally in 1984. This invasion has been negatively affecting the sub-littoral ecosystem of the Mediterranean. One of the important reasons for its success in the Mediterranean is its secondary toxic metabolite called caulerpenyne (CPN). Furthermore, CPN has anti-proliferative and apoptotic activities, therefore, CPN can be considered as a potential native source in cancer therapy. For that reason, modeling this metabolite might be of importance. Increase and decrease of the CPN level before reaching the critical level can be expressed by means of a queueing system in which the number of 'customers' increases and decreases. In fact, production of CPN shows fluctuations for many environmental reasons, which allow us to apply queueing theory. In the present study, the expected time to reach the maximum caulerpenyne level was analyzed and evaluated using queueing theory.

Keywords: Arrival rate; Caulerpenyne; Classical ballot theorem; Queueing theory.

Introduction

The killer alga, *Caulerpa taxifolia* (Vahl) C.Agardh (Ulvophyceae, Caulerpales), is one of most studied invader species in the Mediterranean Sea, where it was accidentally introduced in 1984 (MEINESZ & HESSE, 1991). Since then, *C. taxifolia* has colonized large areas and is continuing its invasion. 'With its highly toxic defense cocktails, it is rarely devoured by herbivores, thus facilitating its limitless spread' (MADL & YIP, 2006). One of its toxic metabolites is caulerpenyne (CPN). The effects of CPN have been shown on some organisms and it may

even slow some cancers (BARBIER *et al.,* 2001; FISCHEL *et al.,* 1985; GALGANI *et al.,* 1996; LEMÉE *et al.,* 1993). Anti-proliferative and also apoptotic activities against some neuroblastoma cell lines by extracts which contain CPN and CPN-derivatives obtained from *Caulerpa racemosa* var.*cylindracea* were also shown (CAVAS *et al.,* 2006). Therefore, CPN is considered to be an important parameter in the invasion of *C. taxifolia* in the Mediterranean. On the other hand, production of *caulerpenyne* by *C. taxifolia* shows some increasing and decreasing fluctuations dependent on variables such as season, nutrients, solar light and the number and variety of other macrophytes (AMADE & LEMÉE, 1998; DUMAY *et al.,* 2002).

There are two important reasons for modeling CPN production in *C. taxifolia;* first, inasmuch as it negatively affects the sub-littoral ecosystem of Mediterranean, especially fishing, knowing the trend of CPN production is of great importance for ecological protection studies; second, since CPN has anti-proliferative and apoptotic activities, knowing when *C. taxifolia* reach the maximum CPN level is also important in any purification study.

Queueing theory is the study of waiting and waiting lines that deals with random input and stochastic service. The study of queues examines the performance of systems and calculates values including the average number of customers in system, the average waiting time in system and the average queue length (TAHA, 1997). In recent years, applications of queueing theory have increased in analyzing clinical and ecological problems. In early studies, POWERS & LACKEY (1975) investigated queueing theory in ecosystem domains. Pharmacokinetics was analyzed in terms of queueing systems by BRILL & MOON (1980). Queueing models have also been applied to the study of various physiological problems (ARUN, 2002); in this way, one can reveal a measure of organ (or sub-organ) function (ARUN, 2000). Beside this, applications of queueing theory in different scientific fields have appeared in areas such as: planning and management techniques in radiology (ROSENQUIST, 1987); study of alcohol intake and removal of its adverse effects from the body (WU, 1998a); applications to inhalation toxicology (WU, 1998b). Queueing models have been used to investigate irradiated cells by MYANISKOVA *et al.* (1996). One application of queueing theory was the assessment of cholesterol levels (SCHELL, 1994). In a very recent study, invasion of *C. taxifolia* has been modeled for patch growth (using stolon extension) and reproduction (using asexual fragmentation and reattachment) (RUESINK & COLLADO-VIDES, 2006). Recently, queueing theory was applied to the relationship between insulin levels and number of insulin receptors. It was concluded that queueing analysis may identify the etiological origins of some insulin-based metabolic disorders (KANDEMIR-CAVAS & CAVAS, 2007).

Since there is inherent uncertainty in future CPN production by *C. taxifolia* and the CPN level may increase or decrease just like the number of customers in a queue, the expected time to reach the maximum CPN produced by *C. taxifolia* has been investigated in this preliminary study using queueing theory. Having examined the available literature, the present paper is the first attempt at using queueing theory on *C. taxifolia* invasion.

Material and Methods

The most commonly analyzed queue is the so-called M/M/1 queue, where the three sections refer to the inter-arrival time distribution, the service time distribution, and the number of servers. This model has been used in many different situations.

In this study, we use the classical ballot theorem which has been applied successfully to queueing by TAKACS (1967) in order to find the distribution of the number of customers served in a busy period for an M /M/1 queue. The following notation is taken from (SCHELL, 1994).

Notations and mathematical expressions of model

λ : The arrival rate. A single unit increase in the CPN level, is equivalent to the arrival of one customer in a single-server queue.

μ : The service rate. A single unit decrease in CPN levels (from any factors) can be considered as a service completion of one customer, who leaves the queue.

A path is a sequence of steps. Consider a path from (0, 0) to point (n, x).

Let u be the number of up steps.

Let d be the number of down steps. So u+d=n and u-d=x. Both u, d are non-negative integers.

Let B_i be the probability that starting at $Y=i$ (any level) the path will reach maximum level x , before reaching level $Y=0$.

Let the probability of an up step be

$$p=\frac{\lambda}{\lambda+\mu}\ . \tag{1}$$

Let the probability of a down step be q so $p+q=1$ and

$$q=\frac{\lambda}{\lambda+\mu}\ . \tag{2}$$

Let n be the number of steps in a particular path.

Starting at level $Y=i$, the probability that a path reaches $Y=x$ before reaching $Y=0$, where $i=1,...,x-1$ is given by the solution to the Gambler's Ruin Problem (WEISSTEIN, 2006).

$$B_i=\begin{cases}\dfrac{1-\left(\dfrac{q}{p}\right)^i}{1-\left(\dfrac{q}{p}\right)^x} & if\ p\neq\dfrac{1}{2}\\[2ex] \dfrac{i}{x} & if\ p=\dfrac{1}{2}\end{cases} \tag{3}$$

$$D_i=1-B_i. \tag{4}$$

Here D_i is the probability that starting at level $Y=i$, the path will reach $Y=0$ (minimum level) before reaching the line $Y=x$.

Define a trial to be a path of at least one step starting at *0* and ending at *0* or x, whichever occurs first. Let P be the probability that a trial ends at x. Let X be the total number of trials required for a path starting at $Y=0$ to eventually reach $Y=x$.

Then

$$E(X)=\frac{1}{P} \tag{5}$$

where

$$P=B_1. \tag{6}$$

Define an up trial to be a trial that starts at *0* and ends at x. Then P is the probability of an up trial. Define a down trial to

be a trial that starts at *0* and ends at *0*. Let Q be the probability of a down trial. Then

$$Q=1-P. \tag{7}$$

Let W be the number of down trials among the X total trials to reach x. Then

$$W=X-1. \tag{8}$$

So $E(W)$, the expected number of down trials required for a path starting at *0* to eventually reach x is

$$E(W)=\frac{1}{P}-1. \tag{9}$$

We call a path that starts at *0* and ends at x (allowing it to return many times to 0 before reaching x) a complete path.

Let Z be the total number of steps in a complete path. We used the two-sided ballot theorem (SCHELL, 1994) in order to find $E(Z)$. From SCHELL (1994), $E(Z)$ is expressed as follows

$$E(Z)=\sum_{n=2}^{\infty}\frac{n}{P}\left[N^{A_0B_x}_{(0,0)(n,x)}\right]p^{a-1}q^{b}+$$
$$+\sum_{n=2}^{\infty}\frac{n}{P}\left[N^{A_0B_x}_{(0,0)(n,0)}\right]p^{\frac{n}{2}-1}q^{\frac{n}{2}} \tag{10}$$

where a and b are defined by

$$a+b=n$$
$$a-b=x, \tag{11}$$

where $N^{A_0B_x}_{(0,0)(n,x)}$ (for x>0) is the number of paths from *(0,0)* to *(n, x)* which stay strictly between the lines $Y=0$ and $Y=x$ until the n-th step, and where $N^{A,B}_{(0,0)(n,0)}$ is the number of paths from *(0,0)* to *(n,0)* which stay strictly between the lines $Y=0$ and $Y=x$ until the n-th step.

We define C_i below. In some special cases, we find

$$N^{A_0B_x}_{(0,0)(n,x)}=C_1 \quad \text{if } n<3x, \tag{12}$$

$$N^{A_0B_x}_{(0,0)(n,x)}=C_1+C_3 \quad \text{if } n<5x. \tag{13}$$

But in the general case, the formulas used are

$$N^{A_0B_x}_{(0,0)(n,x)}=\sum_{i=1}^{\infty}C_{2i-1} \quad ,n,\ x\in Z,\ n\geq 2 \tag{14}$$

and

$$N^{A_0B_x}_{(0,0)(n,0)}=R-\sum_{i=1}^{\infty}C_{2i} \qquad \text{if } n\geq 2 \tag{15}$$

where

$$R=\frac{(n-2)!}{\left(\frac{n}{2}\right)!\left(\frac{n}{2}-1\right)!} \tag{16}$$

if n is even and *0* otherwise

$$C_i=\begin{cases}\dfrac{(n-2)!\left((ix)^2-n\right)}{\left(\frac{n+ix}{2}\right)!\left(\frac{n-ix}{2}\right)!}\\ 0\end{cases} \tag{17}$$

for $n\geq ix$ and $n+ix$ even, *0* otherwise.

Finally, the expected total time required for a path starting at $Y=0$ to eventually reach $Y=x$ is as follows

$$E(S)=E(Z)E(T) \tag{18}$$

where $T=T_i$ is the time to complete the i^{th} step in a path and

$S=\sum_{i=1}^{Z}T_i$ is the total time required for a path starting at $Y=0$ to eventually reach $Y=x$.

Results

In our queueing system, the arrival rate does not depend on the number of customers in the system and we assume that each trial is independent of the others. The CPN level reached by *C. taxifolia* increases and decreases due to several factors. In our analysis, we pool all factors that cause an increase in the level, which are combined as an arrival rate λ. All factors which cause a decrease in the level are combined as a service rate μ.

In this study, the minimum and maximum CPN levels were assumed as *0* and *12 mg/g* fresh weight, respectively.

As illustrated in Figure 1, the model of this process is defined as a complete path (SCHELL, 1994) which starts at *(0,0)* and ends at critical point say $Y=x$, where $x=12$ mg / g is the dangerous point for CPN level. This complete path

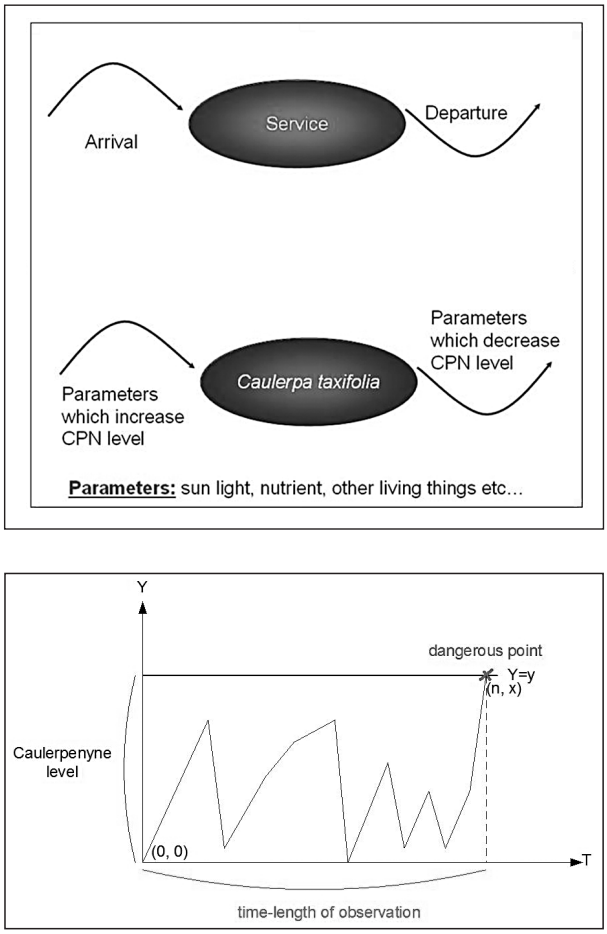

Fig. 1: a) Similarity between queueing system and CPN production in *C.taxifolia.* b) Schematic diagram of a path which starts from (0, 0) up to dangerous point (n, x).

starts from $Y=0$ and may return to the line $Y=0$ before it reaches the critical level $Y=12$ mg / g. This is similar to a queueing system because when a customer arrives in the system, the number of customers increases, when a customer leaves the system after service, the number of customers decreases. Therefore, the fluctuations of the amount of CPN can be thought of as a queueing model which changes from $(0, 0)$ up to point (n, x) where $x=12$ mg / g is assumed in our model.

In our study, we also assume λ and μ as *3* and *2* mg/g wet weight per month, respectively.

Then, from Eq. (1), $p=0.6$ and from Eq. (2), $q=0.4$ are obtained.

Next, we find the probability of an up-trial given in Eq. (6). From Eq. (3), the probability (B_1) that starting at $Y=1$ the path will eventually reach $Y=12$ (the assumed critical point), where $i=1$, is found to be $B_1=0.336$. By Eq. (6), $P=0.336$.

From Eq. (4), D_1 is found to be 0.664. According to Eq. (7), the probability of a down trial ending at 0 is found to be *0.664*.

From Eq. (5), the expected total number of trials required for a path starting at $Y=0$ to eventually reach $Y=12$ is $E(X) = 2.976 \cong 3$ (*2* down trials + *1* up trial).

From Eq. (14), the number of paths from $(0,0)$ to $(n,12)$, which stay strictly between the line $Y=0$ and $Y=12$ can be found for any specified value of n.

From Eq. (15), the number of paths from $(0,0)$ to $(n,0)$, which stay strictly between the lines $Y=0$ and $Y=12$, can be found.

Next, the values above are used in order to find the expected total number of steps required for a path starting at $Y=0$ to eventually reach $Y=12$ using Eq. (10). MATHEMATICA 5 software can solve for the expected number of steps. The expected time for a one step increase or decrease is assumed to be one month. Then, $E(T)=1$. Therefore, from Eq. (18), the expected total time required for a path starting at $Y=0$ to eventually reach $Y=x$ is approximately *44.88* months (3.74 years).

Discussion

C. taxifolia continues its invasion in the Mediterranean and has already reached the American coastline through the ballast waters of ships (MADL & YIP, 2006). CPN produced by *C. taxifolia* shows some fluctuation during adaptation to a new habitat. This situation allows the application of queueing theory. In order to estimate the expected total time to reach maximum CPN level by *C. taxifolia,* we used queueing theory in this preliminary study. As far as we know, no published material exists in the literature on the estimation of CPN production by using such mathematical or statistical models. In our study, we assumed the CPN levels as *0* and *12* mg/g wet weight as minimum and maximum levels, respectively, since CPN did not reach levels over *12* mg/g wet weight (JUNG *et al.,* 2002). We accepted *12* as the critical point. The probability of an up-step and a down-step are not equal. This affects the time that it takes for the CPN concentration to increase during the establishment of *C. taxifolia.* We also found that the probability of an up-trial is *0.336.* This result shows that the CPN level will not reach its maximum levels easily. One reason might be that this species may decrease its CPN production after its adaptation to new habitat. We also found the expected total number of trials required for a path start-

ing at *Y=0* to eventually reach the maximum point is *12*. This result may be confirmed by the fluctuation in CPN levels published by AMADE & LEMÉE (1998). The result clearly shows that in order to reach the maximum CPN level, there must be a large number of decreases in the future. The expected number of total steps required for a path starting at *Y=0* to eventually reach *Y=12* was approximately found as *44.88* months (as 1 month was assumed as observation time unit in this study). However, monthly or annual evaluations are strongly warranted to check the parameters of the model, and to check the appropriateness of the model itself. In addition, environmental parameters are affected by such conditions as the greenhouse effect and global warming, so the parameters might change.

Another invasive species of *Caulerpa* genus is *C. racemosa* var. *cylindracea* which has also widely invaded the sub-littoral ecosystems of the Mediterranean Sea. CPN values in *C. racemosa* var. *cylindracea* change depending on season (CAVAS & YURDAKOC, 2005). These data confirm our mathematical model for *C. taxifolia.*

In conclusion, mathematical and statistical theorems represent appropriate tools to estimate the effects of an invading species on the ecosystem. Queueing theory is only one of the many possible mathematical models; of course, other models may show very different results, depending on their underlying assumptions.

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References

AMADE, P. & LEMÉE, R., 1998. Chemical defence of the Mediterranean alga *Caulerpa taxifolia:* variations in caulerpenyne production. *Aquatic Toxicology,* 43: 287–300.

ARUN, C.P., 2000. Queueing and inventory theory in clinical practice: application to clinical toxicology. *Annals of the New York Academy of Sciences,* 919: 284–287.

ARUN, C.P., 2002. Queue paradigm formulation for the effect of large-volume alcohol intake on the lower urinary tract. *Annals of the New York Academy of Sciences,* 957: 292–294.

BARBIER, P., GUISE, S., HUITOREL, P., AMADE, P., PESANDO, D., BRIAND, C. & PEYROT, V., 2001. CPN from Caulerpa taxifolia has an antiproliferative activity on tumor cell line SK-N-SH and modifies the microtubule network. *Life Sciences,* 70: 415–429.

BRILL, P.H. & MOON, R.E., 1980. Application of queueing theory to pharmacokinetics. *Journal of Pharmacological Sciences,* 69: 558–560.

CAVAS, L. & YURDAKOC, K., 2005. An investigation on the antioxidant status of the invasive alga *Caulerpa racemosa* var.*cylindracea* (Sonder) Verlaque, Huisman, et Boudouresque (*Caulerpales, Chlorophyta*). *Journal of Experimental Marine Biology and Ecology,* 325: 189–200.

CAVAS, L., BASKIN, Y., OLGUN, N. & YURDAKOC, K., 2006. Antiproliferative and newly attributed apoptotic activities from an invasive marine alga: *Caulerpa racemosa* var. *cylindracea. Journal of Experimental Marine Biology and Ecology,* 339: 111–119.

DUMAY, O., PERGENT, G., PERGENT-MARTINI, C. & AMADE, P., 2002. Variations in caulerpenyne contents in *Caulerpa taxifolia* and *Caulerpa racemosa. Journal of Chemical Ecology,* 28: 343–352.

FISCHEL, J.L., LEMÉE, R., FORMENTO, P., CALDANI, C., MOLL, J.L., PESANDO, D., MEINESZ, A., GRELIER, P., PIETRA, F., GUERRIERO, A. & MILANO, G., 1995. Cell growth inhibitory effects of caulerpenyne, a sesquiterpenoid from the marine alga *Caulerpa taxifolia. Anticancer Research,* 15: 2155–2160.

GALGANI, I., PESANDO, D., PORTHENIBELLE, J., FOSSAT, B. & GIRARD, J.P., 1996. Effect of caulerpenyne, a toxin extracted from Caulerpa taxifolia on mechanisms regulating intracellular pH in sea urching eggs and sea bream hepatocytes. *Journal of Biochemical Toxicology,* 11: 243–50.

JUNG, V., THIBAUT, T., MEINESZ, A. & POHNERT, G., 2002. Comparison of the wound activated transformation of caulerpenyne by invasive and noninvasive Caulerpa species of the Mediterranean, *Journal of Chemical Ecology,* 28: 2091–2105.

KANDEMIR-CAVAS, C. & CAVAS, L., 2007. An Application of Queueing Theory to the Relationship Between Insulin Level and Number of Insulin Receptors. *Turkish Journal of Biochemistry,* 32 (1): 32–38.

LEMÉE, R., PESANDO, D., DURAND-CLÉMENT, M., DUBREUIL, A., MEINESZ, A., GUERRIERO, A. & PIETRA, F., 1993. Preliminary survey of toxicity of the green alga *C. taxifolia* introduced into Mediterranean. *Journal of Applied Phycology,* 5: 485–493.

MADL, P. & YIP, M., 2006. Literature review of *Caulerpa taxifolia.* Contribution for the 31st BUFUS Newsletter, www.sbg.ac.at/ipk/avstudio/pierofun/ct/ct-1.html retrieval date: 22.06.2006.

MEINESZ, A. & HESSE, B., 1991. Introduction et invasion de l'algue tropicale *C.taxifolia* en Méditérranée Nord-Occidentale. *Oceanologica* Acta, 14: 415–426.

MYASNIKOVA, E.M., RACHEV, S.T. & YAKOVLEV, A.Y., 1996. Queueing models of potentially lethal damage repair in irradiated cells. *Mathematical Biosciences,* 135: 85–109.

POWERS, J.E. & LACKEY, R.T., 1975. Interaction in ecosystems: a queueing approach to modeling. Mathematical Biosciences, 25: 81–90.

ROSENQUIST, C.J., 1987. Queueing analysis: a useful planning and management technique for radiology. *Journal of Medical Systems,* 11: 413–419.

RUESINK JL & COLLADO-VIDES L, 2006. Modeling the increase and control of *Caulerpa taxifolia,* an invasive marine macroalga. *Biological Invasions,* 8: 309–325.

SCHELL, R., 1994. A Queueing Model for Cholesterol. Master's Paper, University of Windsor.

TAHA, H.A., 1997. Operations Research: An introduction. 6th ed., Prentice Hall, Upper Saddle River, NJ.

TAKACS, L., 1967. Combinatorial Methods in the theory of stochastic processes, Wiley, NY.

WEISSTEIN, E.W., 2006. Gambler's Ruin. From MathWorld--A Wolfram Web Resource. http://mathworld.wolfram.com/GamblersRuin.html retrieval date: 12.06.2006.

WU, G., 1998a. Application of queueing theory with Monte Carlo simulation to the study of intake and adverse effects of ethanol. *Alcohol and Alcoholism,* 33: 519–527.

WU, G. 1998b. Application of the queueing theory with Monte Carlo simulation to inhalation toxicology. *Archives of Toxicology,* 72: 330–335.

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