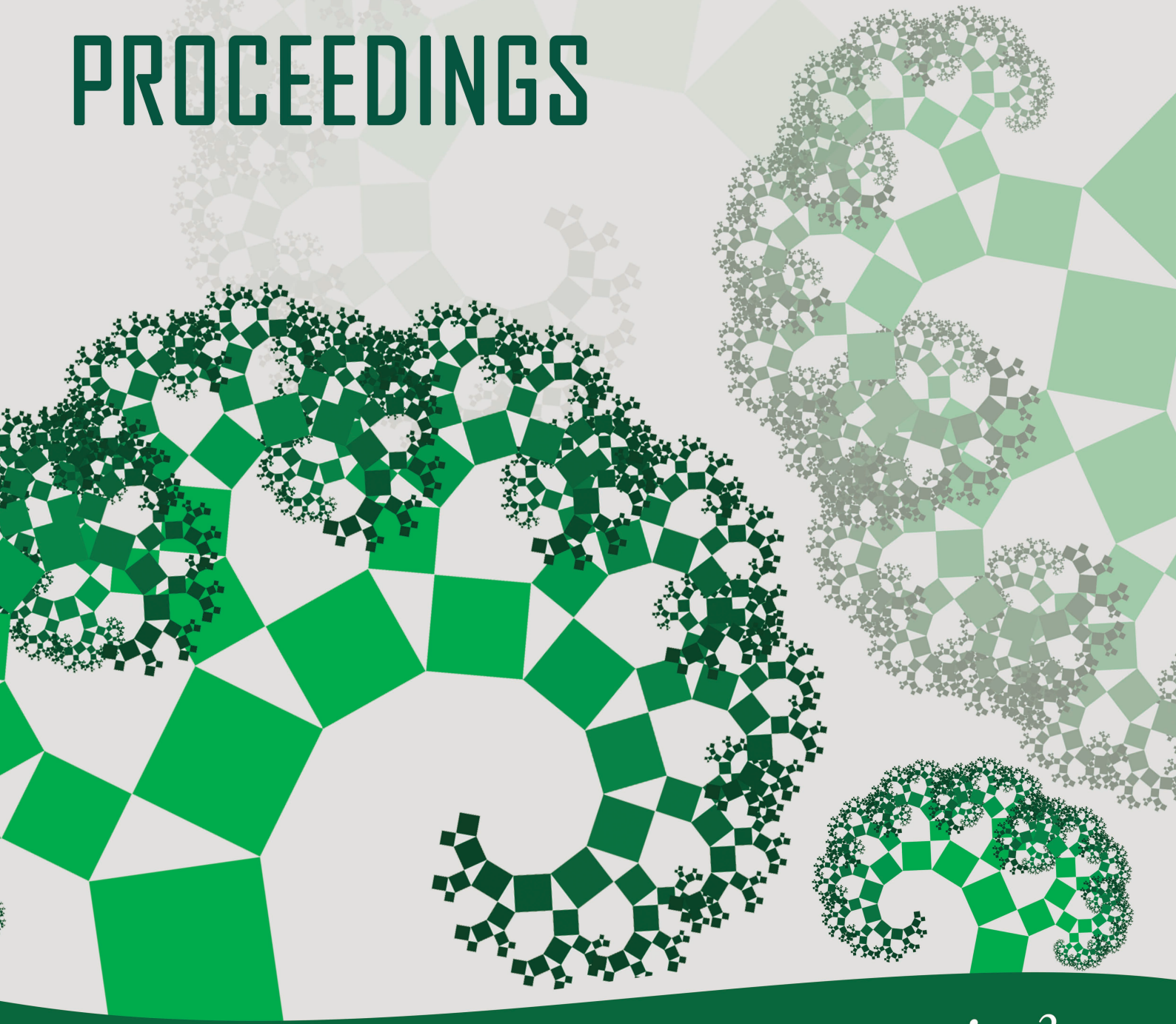
MODELLING FOR ENGINEERING & HUMAN BEHAVIOUR 2022

PROCEEDINGS



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A reaction-diffusion equation to model the population of Candida Auris in an Intensive Care Unit

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1 Introduction

In order to model a population of microorganisms in a given environment through time and space, ordinary differential equations (ODEs) and partial differential equations (PDEs) are, respectively, well studied and very valuable tools. In practice, exact solutions are few and so numerical solutions are often used to describe the dynamic behaviour of the population through time. In order to assert that the numerical solutions are modelling real world phenomena, it is important to calibrate these models with biological and physical data.

In this work, we have applied the Fisher Kolmogorov- Petrovsky–Piskunov (FKPP) equation to model the change in density trough time of Candida Auris (CA) inside an Intensive Care Unit (ICU). The multi-drug resistant yeast CA poses a global threat to the healthcare environment. This model allows us to evaluate the efficacy of well timed cleaning measures on CA population control in the ICU.

2 Methods

2.1 Numerical scheme

The 2-dimensional Fisher Kolmogorov–Petrovsky–Piskunov (Fisher–KPP) model is a reaction-diffusion system that is used to model population growth in a two dimensional coordinate space through time [8], given by the following equation:

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) + ru(1-u), \tag{1}$$

where x and y are the coordinates of a point on a plane, u is the density of the population in $[a,b]\times[c,d]$, $a,b,c,d\in\mathbb{R}$ at a given time t, $D>0$ is the diffusion coefficient and $0\leq r\leq 1$ is the growth rate.

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In this model the variation of the population density u through time is guided by both the diffusion term $D\left(\frac{\partial^2 u}{\partial x^2}+\frac{\partial^2 u}{\partial y^2}\right)$ which models microorganism's expansion in a plane, and the population growth term $ru(1-u)$, which indicates the amount of CA at a given time, with restricted growth, as it is assumed that the environment has a limited amount of resources. However, the closed solution to the FKPP equation is not known. We thus have to solve it numerically.

We first solve the logistic growth equation $\frac{\partial u}{\partial t}=ru(1-u)$ with closed-form solution:

$$u(t)=\frac{u_0\exp(rt)}{u_0(\exp(rt)-1)+1}, \tag{2}$$

where u_0 is the initial normalized quantity of CA in the ICU. In order to estimate the growth rate, r, and the initial value, u_0, we fit the solution to the logistic growth model (2) to CA *in vitro* growth data [2] using least squares estimation method for non-linear functions in R programming language.

We then solve the FKPP model numerically using Matlab. We use explicit finite differences. We buid a 101×101 mesh-grid to model the plane representing the ICU where $x\in\{0,0.1,0.2,\ldots,10\}$ and $y\in\{0,0.1,0.2,\ldots,10\}$, which sets the spatial step to be $h=0.1$. We set Neumann, no flux boundary conditions, where the four corners of the ICU plane have no flux and are maintained to be 0.

We let the time go from 0 to 48 hours with a time step of

$$k=\min\{0.5,0.99\frac{h^2}{4D}\}$$

so that $k<\frac{h^2}{4D}$ in order to guarantee stability in the numerical scheme [5,6].

Our numerical scheme, in matrix form is given by:

$$\begin{aligned} u^{(j+1)} &= \frac{kD}{h^2}Au^{(j)}+u^{(j)}+kru^{(j)}\circ(1-u^{(j)}) \\ u^{(j)'} &= \left[u_{1,1,j}=0,u_{2,1,j},u_{3,1,j},\ldots,u_{N,1,j}=0,\ldots,u_{1,N,j}=0,\ldots,u_{N,N,j}=0\right] \end{aligned} \tag{3}$$

for $j=1,\ldots,T=48$, where A is a $N^2\times N^2$, $N=100$ matrix with all zeroes except at the main diagonal, D_0, off 1 diagonals, D_{-1},D_1 and off 10 diagonals,D_{-N},D_N. Here $\circ$ denotes the Hadamard product (also known as the element-wise product).

$$D_0=(\overbrace{0\ \ldots\ 0}^{N+1}\quad\overbrace{-4\ \ldots\ -4}^{N^2-2N+2}\quad\overbrace{0\ \ldots\ 0}^{N+1})$$

$$D_1=D_{-1}=(\overbrace{0\ \ldots\ 0}^{N}\quad\overbrace{1\ \ldots\ 1}^{N^2-2N-1}\quad\overbrace{0\ \ldots\ 0}^{N})$$

$$D_{-N}=(0\quad\overbrace{1\ \ldots\ 1}^{N-2}\quad 0\ \ 0\quad\overbrace{1\ \ldots\ 1}^{N-2}\quad\ldots)$$

$$D_N=(\overbrace{0\ \ldots\ 0}^{N+1}\quad\overbrace{1\ \ldots\ 1}^{N-2}\quad 0\ \ 0\quad\overbrace{1\ \ldots\ 1}^{N-2}\quad\ldots)$$

This numerical solution has error $O(h+k^2)$.

To numerically solve the Fisher-KPP model, we define our initial condition, so that it both agrees with previous results and literature on microorganism populations, the dynamics of which in biofilms have been shown to share structural aspects with urbanizations [7]:

$$u(x, y, 0) = \exp\{3(-(x-5)^2 - (y-5)^2)\}. \tag{4}$$

We then applied Particle Swarm Optimization (PSO), a bio-inspired optimization algorithm, fist introduced by Kennedy and Eberhar in 1995 [3], to calibrate both the diffusion coefficient D and the growth coefficient r simultaneously. We define as the objective function for the PSO to minimize, the Symmetric Mean Absolute Percentage Error (SMAPE), which has been shown to be a better measure of relative error [9]. SMAPE is defined as:

$$S = \frac{1}{n}\sum_{i=1}^{n} \frac{|z_i - f(t_i)|}{\frac{|z_i| - |f(t_i)|}{2}} \tag{5}$$

where $\{t_1, t_2, \ldots, t_n\}$ is the set of times where CA's $A600nm$ (absorbance at $600nm$ wavelength) was measured [2].

2.2 Introduction of a cleaning factor

The ICU is cleaned regularly by trained staff in order to minimize the spread of any harmful microorganism. To model this and in order to estimate the efficacy of cleaning measures on CA population control and determine potential recommendations, we introduce a cleaning factor into our model. We assume that the ICU is cleaned in a uniform manner. So at times separated by equal intervals, the amount of CA is reduced by some percent at every point (x, y) on the plane. Then when this is introduced to the model, the amount of CA in the ICU at every point (x, y) on the plane and time t is

$$u(x, y, t) = \begin{cases} p\hat{u}(x, y, t), \text{ if cleaning happend at time } t, \\ \hat{u}(x, y, t), \text{ otherwise.} \end{cases} \tag{6}$$

So we periodically reduce the population of CA present in the ICU by a percentage in a homogeneous way.

We then compare the values of

$$M = \frac{max_{i=1,\ldots,n}[\text{total amount of CA at time point i}]}{1,0197 \times 10^2} \tag{7}$$

for different combination of time intervals between cleaning (TI) and cleaning efficacy (CE). This represents the maximum quantity of CA present in the ICU relative to the worse case scenario where the whole ICU is infected $(1,0197 \times 10^2)$.

We choose to vary TI from 2 hours to 10 hours with a one hour increase. Cleaning more often than every $2h$ seems unrealistic and expensive, whereas cleaning less than every $10h$ appears to be too low for a healthcare environment with gravely ill patients who are very susceptible to any sort of infection.

3 Results

The PSO results for SMAPE return the parameter estimates $\hat{D} = 0.4141$, $\hat{r} = 0.3539$. Figure 2 shows the dispersion of CA through the ICU and Figure 1 shows that our total amount of CA at any given time point follows the real data rather well. Using these parameters we then introduced

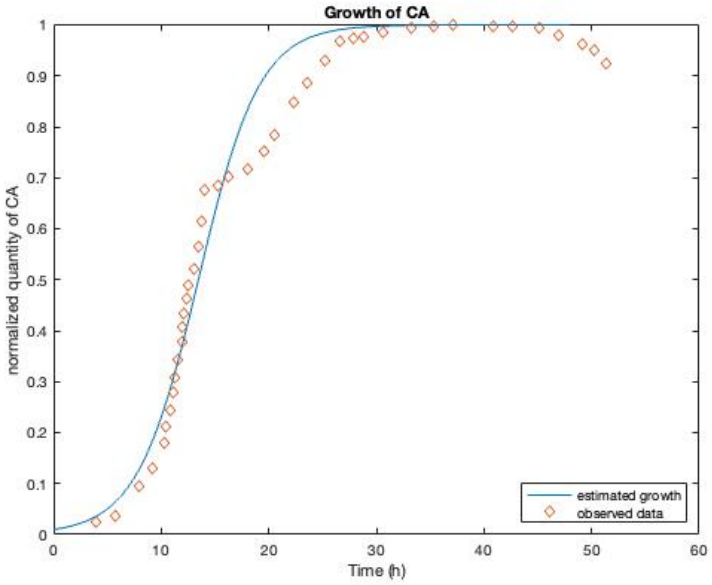


Figure 1: Observed *in vitro* growth of CA (points in orange) and total amount of CA at any given time point (blue line) estimated using PSO and SMAPE error.

the cleaning factor.

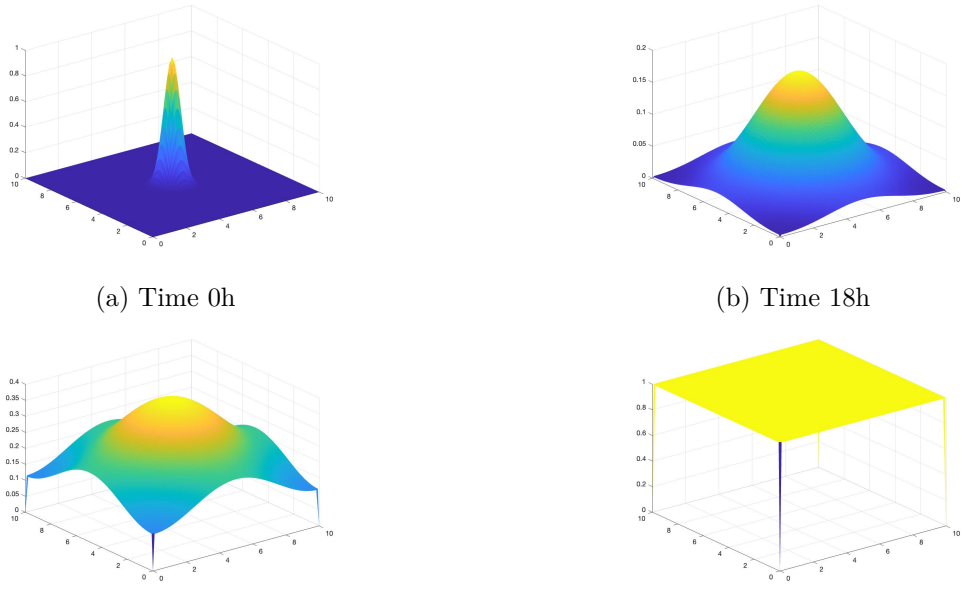
Table 1: Normalized maximum total amount of CA present between 0 and 48 hours (M (7)) for different combinations of TI and CE

		TI (hours)								
		2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
CE (%)	**96.6**	0.0103	0.0103	0.0103	0.0103	0.0103	0.0103	0.0103	0.0103	0.0185
	90	0.0103	0.0103	0.0103	0.0103	0.0103	0.0265	0.1591	0.3573	0.4875
	80	0.0103	0.0103	0.0103	0.0362	0.2644	0.4727	0.7144	0.8023	0.8476
	70	0.0103	0.0103	0.0865	0.3949	0.6540	0.7570	0.8493	0.8951	0.9226
	60	0.0103	0.0702	0.4587	0.6695	0.7918	0.8557	0.9049	0.9341	0.9525
	50	0.0122	0.4161	0.6707	0.7901	0.8631	0.9062	0.9369	0.9564	0.9689

Table 1 compares values of M (7) and shows us that in order to control CA population and keep its amount always under the initial amount present in the outbreak, cleaning of the ICU should be performed at most every $3h$. If cleaning is performed every $3h$ the cleaning efficacy of the agent should be at least 70%. If it is affordable to perform cleaning every $2h$, then the cleaning agent should have an efficacy of at least 60%. For cleaning efficacies of 50% and under, we do not achieve the desired population control.

4 Conclusions

We have built a FKPP reaction-diffusion model, which we solved numerically and then calibrated to real-life data of CA growth. In our simulations, we showed that if cleaning is done often enough, and at a high enough frequency, the maximum amount of CA present in the ICU does not surpass



(a) Time 0h

(b) Time 18h

(c) Time 25h

(d) Time 48h

Figure 2: 3D plots of the FKPP numeric solutions when $\hat{r} = 0.3539,\ \hat{D} = 0.4141$

the initial amount of the outbreak. If cleaning is performed every 3 hours the cleaning efficacy of the agent should be at least 70%. If cleaning is performed every 2 hours, then the cleaning agent should have an efficacy of at least 60%.

There are, however, great limitations in our model and the introduction of the cleaning factor that need to be addressed.

First, our model is calibrated with in-vitro growth of CA which is not equivalent to microbial growth in a health care environment [2]. The ICU is kept at a temperature of 23^oC, whereas the strains in the observed data were incubated at 37^oC, which is a lot closer to the optimal temperature for CA growth. Therefore, we can expect CA growth to be slower in an ICU, approaching a full contamination level at around 48 hours, as mentioned by ICU personnel, rather than 25 hours.

Secondly, our model does not account for the ecological pressures present in the microbial environment such as local extinction and colonization processes as different species compete for resources [4]. It is important to think about how cleaning can affect the environmental competition. Cleaning could perhaps reduce in a more significant way a microorganism that is highly competitive with CA, which would then allow CA access to more resources and accelerate its growth. Some cleaning agents such as H_2O_2 vapor have been shown to be more effective at killing non CA species [1].

Homogeneous cleaning is also an unreasonable assumption. Some of the ICU material cannot be cleaned as in depth as a simple plastic surface. Keyboards, screens, tubes, etc. cannot be always cleaned with all cleaning agents and in a in depth manner.

This model, however, indicates that the efficacy of the cleaning agent and how often the ICU room is cleaned greatly affects how well the yeast can be controlled.

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