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Cauchy-Euler Model, Cellular Automata Simulation of the Rate of Recovery of the Infected Airway from COPD

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Abstract— **Chronic obstructive pulmonary disease (COPD) is associated with the respiratory system. COPD is often treated with inhalers whose two major ingredients are the bronchodilators and the steroids. In this paper we mathematically model the deposition of the inhaled drug on the infected airway into Cauchy-Euler differential equation and use Visual Basic to simulate the evolution of the recovery of the inflamed airway.**

Keywords-component; **COPD; Deposition of Inhaled Drug; Recovery of Infected Airway; Cauchy-Euler Model; Cellular Automata Simulation.**

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with lower respiratory diseases. Other names of COPD are chronic obstructive airway disease (COAD), chronic airflow limitation (CAL) and chronic obstructive respiratory disease (CORD). COPD is caused by noxious particles or gas, smoking in particular, which trigger an abnormal inflammatory response in the lung [1, 2]. The inflammatory response in the larger airways is known as *chronic bronchitis*, which is diagnosed clinically when people regularly cough up sputum. In the alveoli, the inflammatory response causes destruction of the tissues of the lung, a process known as emphysema. The natural course of COPD is characterized by occasional sudden worsening of symptoms called acute exacerbations, most of which are caused by infections or air pollution. COPD refers to chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed [2]. COPD is often treated with inhalers whose two major ingredients are the bronchodilators and the steroids. When bronchodilators are inhaled they open the airways quickly. Inhaled steroids act slowly, but the use of the steroids are essential as they bring the airways back to normal and help reduce the level of inflammation of the airways. And therefore the steroids help reduce the usage of the bronchodilators. If the steroids are not used, then the inflammation continues unhindered and this results in the piling up of the mucus and swelling of the surface of the airway. At this stage, even higher doses of the bronchodilator are of no use as this causes the toxicity to sets in. The serious side effect is the sudden death. The good news is that the death rate decreases by a 54% for every additional canister containing steroids is used [3]. Allergies and allergens, such as food and food additives, pollen, dust mites, cockroaches, bacteria, molls or animal hair can trigger COPD. Another apparent cause is a viral infection; when sufferers catch a virus, it tends to affect their respiratory system, thus further irritating the airways and making COPD more troubling.

Although it must be stated that COPD is never truly cured, it can be well controlled. Good COPD control prevents chronic and troublesome symptoms such as coughing or shortness of breath, reducing the need for quick-relief medications, helping sufferers maintain good lung function, letting them maintain normal activities and sleep through the night. It is possible for the disease to seemingly disappear, but all this means is that it is not causing problems for the time being. Sufferers may go for very long periods without any COPD symptoms, but it is still very important to keep it monitored in case an COPD

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attack rises out of nowhere. This is possible even after years of not showing any symptoms of the disease. Microscopically there is infiltration of the airway walls with inflammatory cells. Inflammation is followed by scarring and remodelling that thickens the walls, narrow downs the airways causing the limitation of airflow (very low FEV_1) [4].

In contrast to asthma, the limitation of airflow is poorly reversible and usually gets progressively worse over time. But, if airflow limitation is fully or substantially reversible, the patient should be treated as for asthma [5]. The natural course of COPD is characterized by occasional sudden worsening of symptoms called acute exacerbations whose frequency may be brought down by the treating such patients with the combination of the inhaled corticosteroid fluticasone propionate (250 mcg) and the long-acting β2-agonist (also known as a bronchodilator) , salmeterol (50 mcg) in a single inhaler (250/50 mcg) [6]. But, The New Zealand Guidelines Group Handbook on COPD also specify giving "200 to 400 mcg salbutamol from MDI and spacer" as a suitable dosage protocol for patients undergoing spirometer test as a diagnostic assessment, in whom COPD is suspected [7].

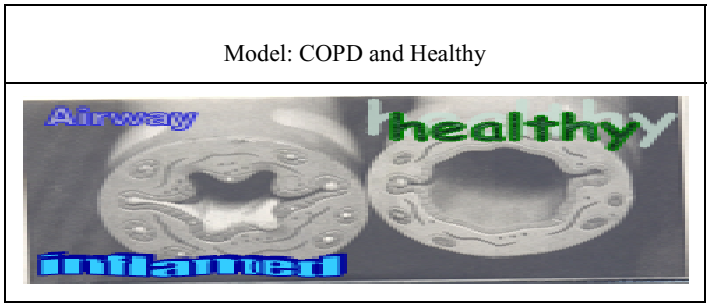


Figure 1. Healthy and infected airways

II. MATHEMATICAL MODELLING

We first model the amount of deposition of the inhaled drug on the inflamed airway into a two dimensional cellular automaton [8] on a square grid. Notable recent work is a respiratory deposition model of an inhaled aerosol bolus by Chien-Wen Huang, Chun Pei and Chien-Hua Huang [9] where the inhaled particle concentration is shown to satisfy a first order partial differential equations. Other works deal with the deposition of the inhaled pollutants on the lungs, see for instance, Hussain, Madl and Khan [10] and the references therein.

Suppose that the COPD patients use inhalers containing the bronchodilator Formoterol Fumarate (FF) and the corticosteroid, Fluticasone Propionate (FP). This drug is being sold as Avessa by Ranbaxy. An Avessa 250 inhaler contains 120 metered doses, and each inhalation releases 250 mcg of FF and 6 mcg of FP into the airway. This 256 mcg of the drug is delivered along the inflamed airway by air playing the role of a "vehicle." Assume that this 256 mcg of the drug contains N number of nanoparticles.

We now take an inflamed airway of length L_a meters. Suppose that this inflamed airway is cut straight across its length and spread as a rectangle with width W_a meters. We divide the airway across its length L_a into L number of equal sub-lengths. We denote an arbitrarily chosen sub-length by l. Then $1 \leq l \leq L$. We divide the airway across its width W_a into W number of equal sub-widths. We denote an arbitrarily chosen sub-width by w. Then $1 \leq w \leq W$. The surface areas of all cells are equal and is given by $(L_a W_a) / (L W)$. There are L W numbers of cells. Each cell is identified by a pair (l, w) for $1 \leq l \leq L$, $1 \leq w \leq W$.

Suppose that the number of nanoparticles (the drug) that enter the inlet of the inflamed airway is N. It is easily understandable that the inhaled "air" acts as a delivery vehicle. Initially all these N nanoparticles pass through the first column.

This first column contains W cells (1,1), (2,1),…,(W,1). Let us denote by D_{wl} the number of nanoparticles that get deposited in the cell (w, l). Therefore the number of nanoparticles that sets in the cells (1,1), (2,1),…,(W,1) respectively are D_{11}, D_{21},…,D_{W1}. Hence the total number of nanoparticles deposited in the first column is $D_{11} + D_{21} + \ldots + D_{W1}$. We denote this number by $D_{1\to W;1}$ and is given by $D_{1\to W;1} = D_{11} + D_{21} + \ldots + D_{W1}$

So the number of nanoparticles that enter the second column = The total number of particles – The number of particles settled in the first column = $N - D_{1\to W:1}$. In a similar manner, if $D_{1\to W:2}$ is the total number of nanoparticles that get deposited in the second column which consists of the cells (1,2), (2,2),…,(W,2), and if we again denote by $D_{1\to W:2} = D_{12} + D_{22} + \ldots + D_{W2}$. Then the number of particles entering the third column is $N - D_{1\to W:1} - D_{1\to W:2}$. Thus the total number (let us denote by T_A) of nanoparticles absorbed by the airway is $T_A = D_{1\to W:1} + D_{1\to W:2} + \ldots + D_{1\to W:L}$. And the number of nanoparticles leaving the airway (denoted by T_{NA}) is $T_{NA} = N - (D_{1\to W:1} + D_{1\to W:2} + \ldots + D_{1\to W:L})$.

A. Cauchy-Euler Equation

For brevity, we suppose that L = W = 1. Following table provides the cumulative amount (in mcg) of the deposed drug in a chosen cell over the period of three months. Here $1 \leq t \leq 6$ is the first month, $7 \leq t \leq 12$ is the second month and $13 \leq t \leq 18$ is the third month. Further one time step assumed equivalent to 10 inhalations in 5 days.

The data is obtained as detailed here: A random number, r, is generated with the help of Normal distribution, N(0,1) and |r| is multiplied by p=0.7. The resulting number p r is then multiplied by the amount 256mcg of the drug. We therefore arrive at the number $r1 = 256 \times 0.7 \times |r|$. These steps are repeated to determine r2, r3,…,r10. Then the arithmetic mean (r1+r2+…+r10)/10 is entered for y(1). And, if we repeat this procedure we will arrive at another number, y2, say. Then y(2) = y(1) + y2. Proceeding in this manner one may generate all the remaining values, viz., y(3), y(4),…,y(18).

TABLE 1. VALUES OF y FOR t =1,2,…,6

t	1	2	3	4	5	6
y	7.4054	21.4446	27.0913	50.0433	52.173	62.2997

TABLE 2. VALUES OF y FOR t =7,8,…,18

7	8	9	10	11	12
68.55	80.7147	85.6859	95.3637	101.148	115.7
13	14	15	16	17	18
121.6	123.3201	127.3662	140.5167	143.955	150.2

The equation for y(t) is obtained using the symbolic manipulation system MATHEMATICA [11]:

$$y(t) = 11.2921\, t - 0.176506\, t^2 + 0.000651194\, t^3. \quad (1)$$

The figure shows the values and the curve for y:

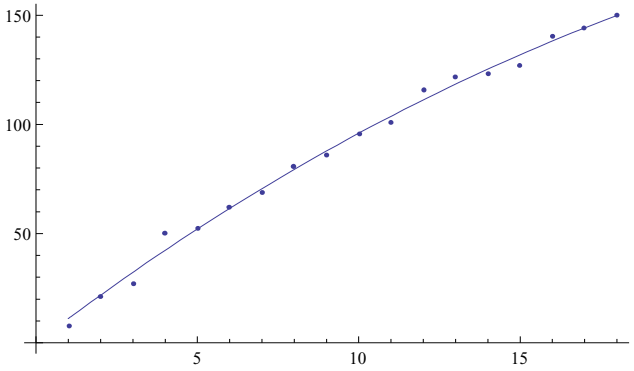


Figure 2. Graph of (1)

We infer from the figure 2 that the value of y at t = 1 is not 7. 4054. To correct this, we write down the the third order Cauchy-Euler differential equation for y(t) [12]:

$$t^3 y'''(t) - 3 t^2 y''(t) + 6 t y'(t) - 6 y(t) = 0. \quad (2)$$

The general solution of (2) is

$$y(t) = a\, t + b\, t^2 + c\, t^3, \quad (3)$$

where *a, b* and *c* are arbitrary constants. By demanding this curve to pass through the point (t=1, y=7.4054) the values of *a, b* and *c* may be fixed. The corrected expression for y(t) and the curve are

$$y(t) = 6.9061\, t + 0.5240\, t^2 - 0.0247\, t^3. \quad (4)$$

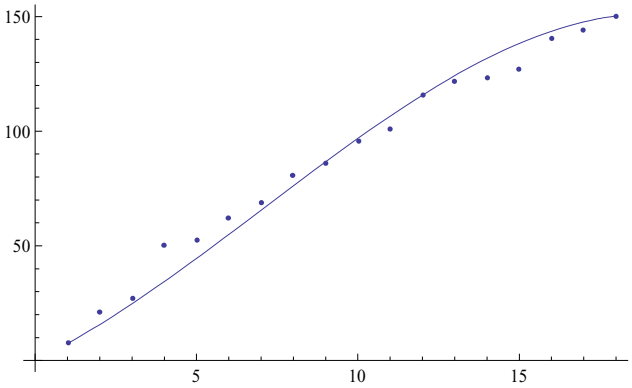


Figure 3. Graph of (4)

The expression (4) for *y(t)* also satisfies the same Cauchy-Euler model (2).

III. VISUAL BASIC SIMULATION

Now we shall explain in detail the simulation using visual basic [13] of the rate of recovery of the infected airway using the two-dimensional cellular automaton on a square grid with von Neumann neighborhood of range 1. The infected airway is divided into 10000 cells with L = W = 100. Certain assumptions are in order so as to carry out the desired simulation in a sensible manner.

- A parameter p ($0 < p \leq 1$) is introduced as the rate of infection.
- Each of the 10000 cells in the two-dimensional cellular automaton is in any one of the four states Sn (n = 1, 2, 3,4): $0 \leq$ S1 < 0.25, $0.25 \leq$ S2 < 0.5 , $0.5 \leq$ S3 < 0.75 and $0.75 \leq$ S4 ≤ 1. The meaning is that the rate of infection of a cell which is in a state S2 is anywhere from 0.25 to 0.5 (the upper boundary value 0.5 is not included). We assign: State 1 – Green; State 2 – Yellow; State 3 – Red; State 4 – Pink.
- A time step, *t*, is inhalation of 60 metered doses. An inhalation of one metered dose contains 256 mcg of the drug.

In order to specify the current status of the infected airway we proceed as follows. We first assume a value for p: p = 0.7 which translates into the fact that nearly 70% of the airway is infected. Then the program is activated to generate random numbers for each cell starting from (1, 1) to (10000, 10000) in a row wise. The state of each cell undergoes a change according to the p-random numbers, i.e., the random numbers multiplied by p. And this is accepted as the current status of the infected airway.

As a next time step, the patient inhales a metered dose of 256 mcg of drug, and these drug particles are also assumed to be deposited in the two dimensional grid and consequently initiate the process of recovery from COPD. As dictated by the cellular automata theory [14--17], a transition rule is imposed to determine the evolution of the states of the cells. The

following transition rule according to von Neumann neighborhood with range r = 1 is applied:

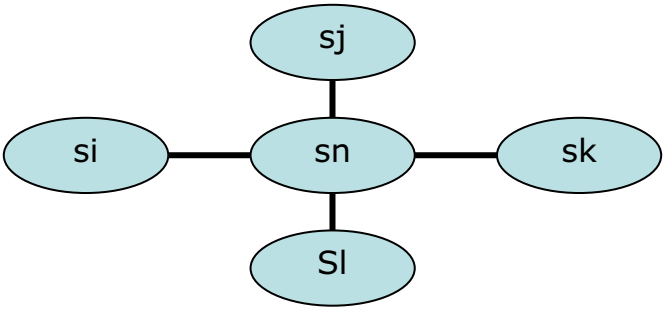


Figure 4. von Neumann neighbourhood with r=1

TABLE 2. TRANSITION RULE

Value of i + j + k + l	n of state Sn
4 to 16	4
3	3
2	2
1	1

A. *Initial State*

The following is the visualization as a cellular automation of the airway with 70% infection. Most of the cells have either pink or red and it shows that the airway is highly infected.

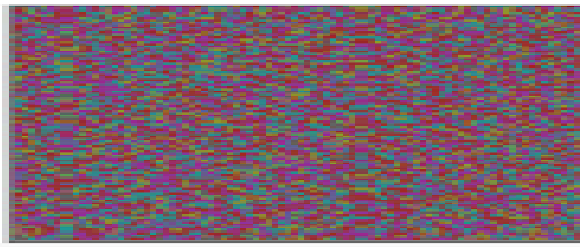
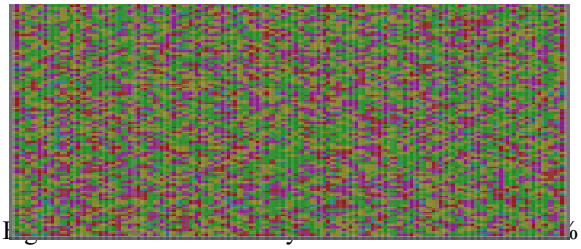


Figure 5. Simulated airway infected with COPD

B. *One Month Treatment*

After one month treatment, i.e., after the inhalation of 120 metered doses of the drug particles the infection level has been brought down under 50% as is evident from the following figure. We may loosely say that the number of cells with pink or red is very much lower that the number of cells with yellow and green.



C. *Two Months Treatment*

After the inhalation of 240 metered doses of the drug particles, the recovery from COPD is appreciable as the following figure reveals that most of the cells are green. And this translates into the fact that the infection is below 25.

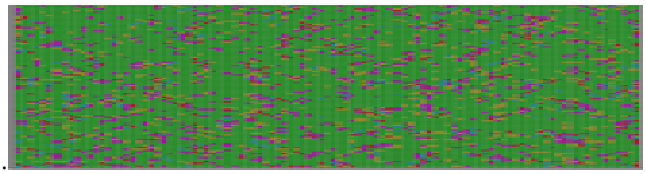


Figure 7. Simulated airway with infection under 25%

D. *Three Months Treatment*

After three month treatment equivalent to the inhalation of 360 metered doses of the drug the airway has almost recovered from COPD and there is only a negligible number of cells have pink.

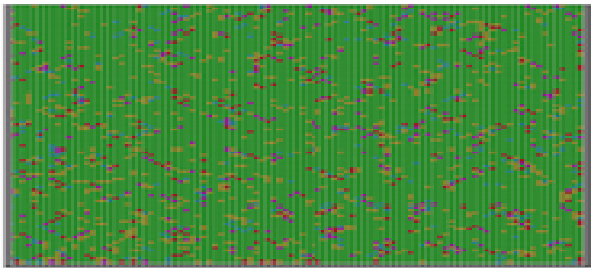


Figure 8. Simulated airway with no infection

The omnipresence of the state S1 indicates that the recovery is 75%.

IV. RESULTS AND DISCUSSIONS

Cauchy-Euler equation (2) modeling the deposition of the inhaled drugs in the form of nanoparticles is derived. Cellular automata with von Neumann neighborhood is used to simulate the recovery of the airway infected by COPD.

We remark that the work is in progress to model the deposition of the drug particles in two cells into a partial differential equation (PDE) with two independent variables. Further work in this direction is of no interest just because if

we consider, for instance, 10 cells, then the model is expected to be a PDE with 10 independent variables! But we have the option of modeling the deposition in ***n*** cells into a dynamical system which will contain ***n*** ordinary differential equations. Then the case ***n*** ∞ may be investigated to yield a PDE as in the theory of dynamical systems. For further readings one may refer the work of Tabor [18].

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