NUMERICAL SOLUTION OF A MATHEMATICAL MODEL OF THE EFFECTS OF HIV/AIDS ON PROGRESSION FROM LATENT TUBERCULOSIS TO INFECTIOUS TUBERCULOSI

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Abstract- In this study, a Mathematical Model on the effects of HIV/AIDS on the progression from Latent Tuberculosis to infectious Tuberculosis was formulated using a modified Susceptible-Infected-Susceptible (SIS) model. Parameters for speedy progression from latently infected tuberculosis to infectious tuberculosis resulting from immunosuppressive condition caused by HIV/AIDS were incorporated into the model given rise to a system of four non-linear differential equations which was solved using fourth order Runge-Kutta method and the resulted algorithm was coded using Mapple software. The result shows that Tuberculosis progress faster from Latent Tuberculosis to Infectious Tuberculosis when there is high compromise of immune system of TB patients by HIV. Effective administration of Antiretroviral drugs to HIV patients will decrease the rate of progression from Latent Tuberculosis to Infectious Tuberculosis. However, high Latent TB treatment was also found to eradicate Tuberculosis with time despite the immunosuppressive condition caused by HIV.

Key words- HIV/AIDS; Immune system; Latent Tuberculosis; Infectious Tuberculosis; Runge-Kutta method.

I. INTRODUCTION

Tuberculosis is the most common opportunistic disease and cause of mortality in AIDS patients in developing countries accounting for approximately 25% of all HIV-associated deaths each year. In the presence of HIV, TB is associated with substantially higher case fatality rates and it is the commonest notified cause of death. The mortality in TB-HIV co-infected patients is usually because of complications from overwhelming TB disease or impaired immunity from advancing AIDS. Effective treatment for TB and HIV exists, but treating both diseases simultaneously is challenging [1].

Despite World Health Organization (WHO) guidelines supporting TB-HIV co-treatment, antiretroviral therapy (ART) initiation is often deferred until TB treatment completion because of concerns of potential drug interactions between rifampicin and specific antiretroviral drugs, clinical deterioration from immune reconstitution inflammatory Syndrome (IRIS), overlapping side-effects, high pill burden compromising treatment adherence, and programmatic challenges. However, delays ART initiation may result in AIDS- related illness and death[2].

The goal of managing TB-HIV co-infected patients is to strike an optimal balance between the risks and benefits of increased mortality associated with delaying ART initiation to later in the course of TB therapy, against the morbidity and mortality burden associated with early ART initiation [3].

The classic symptoms of active TB infection are chronic cough with blood-tinged sputum, fever, night sweat, and weight loss. Infection of other organs causes a wide range of symptoms [3]. Tuberculosis develops when Mycobacterium tuberculosis bacteria are inhaled into lungs. The infection usually stays in the lungs. But the bacteria can travel through the bloodstream to other parts of the body [1]. An initial infection can be so mild that you don't even know you have an infection. In a person who has a healthy immune system, the body usually fights the infection by walling off (encapsulating) the bacteria into tiny capsules called tubercles. The bacteria remain alive but cannot spread to surrounding tissues or other people. This stage is called latent TB and most people never go beyond it [4].

Efforts have been made in the past to use mathematical models to predict the effect of Anti-retroviral therapy and tuberculosis treatment and control. Enagi [5], Enagi and Ibrahim [6], Enagi and Ibrahim [7], and Enagi [8] presented four deterministic compartmental mathematical models for the dynamics of tuberculosis taking into consideration the effect of HIV/AIDS on immune system and administration of BCG vaccines as immunity against infection. In another study Enagi [9], developed a software using Visual Basic Version 6 to carry out comparative analysis of Enagi[5], Enagi and Ibrahim [6], Enagi and Ibrahim [7], and Enagi [8] to determine the most efficient model for eradicating Tuberculosis from Nigeria. He concluded that, Model with only infectious TB treatment can only at best reduce the epidemic if the contraction rate is very low

and that explains the steady rise in the reported cases of TB in Nigeria over the years. The National Tuberculosis and Leprosy control Programme was only concentrating on Infectious TB treatment. Model with immunization and infectious TB treatment was able to eradicate Tuberculosis when there was 90% immunization coverage alongside with very low contraction rate within two decades. Introduction of Latent TB treatment into model with immunization and infectious TB treatment guaranteed total eradication of TB in twelve years. Hence this model turned out to be the best model from their study to be adopted in order to ensure that Tuberculosis be completely eradicated from Nigeria within the next one and halve decades.

In this study, we extended our work in Enagi [9] by obtaining numerical solutions of the mathematical model on the effects of HIV/AIDS on the progression from Latent Tuberculosis to infectious Tuberculosis.

II. MATERIALS AND METHODS

2.1 Model development

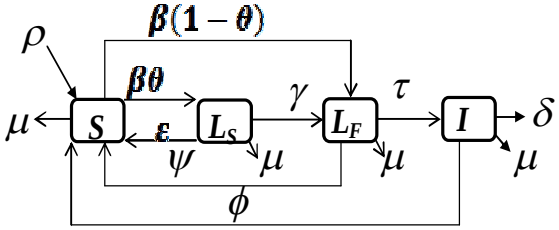


Figure 1. Schematic diagram of the model

$S(t)$ is the number of susceptible individuals at time t, $L_s(t)$ is the number of latently infected individuals with slow progression rate to latently infected individual with fast progression class at time t, $L_F(t)$ is the number of latently infected individuals with fast progression rate to infectious class at time t, $I(t)$ is the number of infectious individuals at time t, μ is the Natural death rate, β is the Tuberculosis instantaneous incidence rate per susceptible, θ is the proportion of infection instantaneous incidence rate with slow progression rate to infectious tuberculosis, γ is the movement rate from latent class with slow progression rate to latent class with fast progression rate. τ is the movement rate from latent class with fast progression rate to infectious class.δ is the Tuberculosis induced death rate, ε is the recovery rate of latent class with slow progression. ψ is the recovery rate of latent class with fast progression and φ is the recovery rate of infectious class. We assumed that there is constant recruitment into the susceptible class denoted by ρ.

2.2 The Model Equations

The model is represented by the following system of four non-linear ordinary differential equations

$$\frac{dS}{dt} = \rho - \mu S - \beta\theta IS - \beta(1-\theta)IS + \varepsilon L_S + \psi L_F + \varphi I \quad (2.1a)$$

$$\frac{dL_S}{dt} = \beta\theta IS - (\mu + \gamma + \varepsilon)L_S \quad (2.1b)$$

$$\frac{dL_F}{dt} = (1-\theta)\beta IS + \gamma L_S - (\mu + \tau + \psi)L_F \quad (2.1c)$$

$$\frac{dI}{dt} = \gamma L_F - (\mu + \delta + \varphi)I \quad (2.1d)$$

3.1 Numerical Solution of the Model Equations using 4th order Runge-Kutta Method

Ordinary differential equations are either solved analytically or numerically. The numerical methods for solving first-order differential equations include Euler's method, Euler's Cauchy's method, and Runge-Kutta Method. The fourth-order method is undoubtedly the most popular of all Runge-Kutta methods. Indeed it is frequently referred to, somewhat loosely, as 'the fourth-order Runge-Kutta method [10]

$$\left.\begin{aligned} y_{n+1} - y_n &= \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4) \\ k_1 &= f(x_n, y_n) \\ k_2 &= f\left(x_n + \frac{1}{2}h, y_n + \frac{1}{2}hk_1\right) \\ k_3 &= f\left(x_n + \frac{1}{2}h, y_n + \frac{1}{2}hk_2\right) \\ k_4 &= f(x_n + h, y_n + hk_3) \end{aligned}\right\} \quad (3.1)$$

This method was first proposed by Runge and subsequently developed by Kutta and Heun. The fourth order Runge-Kutta method is widely used due to its high degree of accuracy (efficiency), being numerically stable and easy to program [11]. Furthermore, no formulae for the higher derivatives need to be computed nor do they have to be in the program. This makes the method more acceptable for solution of model equations which are first order coupled nonlinear initial value ordinary differential equations. We thus, implemented Runge-Kutta fourth order method to find the numerical solutions of (2.1) passing through the initial value conditions of the variables.

To apply the Runge-Kutta method to system (2.1), we let

$$\left.\begin{aligned} y_i^1 &= S \\ y_i^2 &= L_s \\ y_i^3 &= L_F \\ y_i^4 &= I \\ i &= 0, 1, 2, 3, \ldots \end{aligned}\right\} \quad (3.2)$$

with initial conditions

$$\left.\begin{aligned} y_i^1 &= S(0) \\ y_i^2 &= L_s(0) \\ y_i^3 &= L_F(0) \\ y_i^4 &= I(0) \end{aligned}\right\} \quad (3.3)$$

Applying the fourth order Runge-Kutta method to (2.1a), we have

$$y_{i+1}^1 = y_i^1 + \frac{1}{6}(m_1^1 + 2m_2^1 + 2m_3^1 + m_4^1) \qquad i = 0, 1, 2... \qquad (3.4)$$

where,

$$\left.\begin{aligned} m_1^1 &= hf_1(t_i, y_1^1, y_1^2, y_1^3, y_1^4) = h(\rho - \beta\theta y_1^1 y_1^4 + \varepsilon y_1^2 + y_1^3 + \varphi y_1^4 - \mu y_1^1) \\ m_2^1 &= hf_1\left(t_i + \frac{1}{2}h, y_i^1 + \frac{1}{2}m_1^1, y_i^2 + \frac{1}{2}m_1^2, y_i^3 + \frac{1}{2}m_1^3, y_i^4 + \frac{1}{2}m_1^4,\right) \\ m_3^1 &= hf_1\left(t_i + \frac{1}{2}h, y_i^1 + \frac{1}{2}m_2^1, y_i^2 + \frac{1}{2}m_2^2, y_i^3 + \frac{1}{2}m_2^3, y_i^4 + \frac{1}{2}m_2^4,\right) \\ m_4^1 &= hf_1(t_i + h, y_i^1 + m_3^1, y_i^2 + m_3^2, y_i^3 + m_3^3, y_i^4 + m_3^4,) \end{aligned}\right\} \quad (3.5)$$

Applying the fourth order Runge-Kutta method to (2.1b), we have

$$y_{i+1}^2 = y_i^2 + \frac{1}{6}(m_1^2 + 2m_2^2 + 2m_3^2 + m_4^2) \qquad i = 0, 1, 2... \qquad (3.6)$$

where,

$$\left.\begin{aligned} m_1^2 &= hf_2(t_i, y_1^1, y_1^2, y_1^4) = h(\beta\theta y_1^1 y_1^4 + k_1 y_1^2) \\ m_2^2 &= hf_2\left(t_i + \frac{1}{2}h, y_i^1 + \frac{1}{2}m_1^1, y_i^2 + \frac{1}{2}m_1^2,, y_i^4 + \frac{1}{2}m_1^4,\right) \\ m_3^2 &= hf_2\left(t_i + \frac{1}{2}h, y_i^1 + \frac{1}{2}m_2^1, y_i^2 + \frac{1}{2}m_2^2,, y_i^4 + \frac{1}{2}m_2^4,\right) \\ m_4^2 &= hf_2(t_i + h, y_i^1 + m_3^1, y_i^2 + m_3^2,, y_i^4 + m_3^4,) \end{aligned}\right\} \quad (3.7)$$

Applying the fourth order Runge-Kutta method to (2.1c), we have

$$y_{i+1}^3 = y_i^3 + \frac{1}{6}(m_1^2 + 2m_2^2 + 2m_3^2 + m_4^2) \qquad i = 0, 1, 2... \quad (3.8)$$

where,

$$\left.\begin{aligned} m_1^3 &= hf_3(t_i, y_1^1, y_1^2, y_1^3, y_1^4) = h[(1-\theta)\beta y_1^1 y_1^4 + y_1^2 - k_2 y_1^3] \\ m_2^3 &= hf_3\left(t_i + \frac{1}{2}h, y_i^1 + \frac{1}{2}m_1^1, y_i^2 + \frac{1}{2}m_1^2, y_i^3 + \frac{1}{2}m_1^3, y_i^4 + \frac{1}{2}m_1^4,\right) \\ m_3^3 &= hf_3\left(t_i + \frac{1}{2}h, y_i^1 + \frac{1}{2}m_2^1, y_i^2 + \frac{1}{2}m_2^2, y_i^3 + \frac{1}{2}m_2^3, y_i^4 + \frac{1}{2}m_2^4,\right) \\ m_4^3 &= hf_3(t_i + h, y_i^1 + m_3^1, y_i^2 + m_3^2, y_i^3 + m_3^3, y_i^4 + m_3^4,) \end{aligned}\right\} \quad (3.9)$$

Applying the fourth order Runge-Kutta method to (2.1d), we have

$$y_{i+1}^4 = y_i^4 + \frac{1}{6}(m_1^2 + 2m_2^2 + 2m_3^2 + m_4^2) \qquad i = 0, 1, 2... \qquad (3.10)$$

where,

$$\left.\begin{aligned} m_1^4 &= hf_4(t_i, y_1^3,, y_1^4) = h(\tau y_1^3 - k_3 y_1^4) \\ m_2^4 &= hf_4\left(t_i + \frac{1}{2}h, y_i^3 + \frac{1}{2}m_1^3,, y_i^4 + \frac{1}{2}m_1^4,\right) \\ m_3^4 &= hf_4\left(t_i + \frac{1}{2}h, y_i^3 + \frac{1}{2}m_2^3,, y_i^4 + \frac{1}{2}m_2^4,\right) \\ m_4^4 &= hf_4(t_i + h, y_i^3 + m_3^3, y_i^4 + m_3^4,) \end{aligned}\right\} \quad (3.11$$

and h is the step size.

III. RESULTS OF NUMERICAL SIMULATION OF THE MODEL EQUATIONS

The result of the Runge-Kutta scheme (Equations 3.4 to 3.11) was coded using a mathematical software (Maple 14) (Appendix). From the available literature, we adopted the following values for the parameters.

Recruitment rate $\rho = 0.045$ [12].

$Natural\ death\ rate\ \mu = 0.014$ [12].

Tuberculosis instataneous incident rate $\beta = 0.001$ [13].

$Recovery\ rate\ of\ L_s(t)\varepsilon = 0.1$ [13].

$Recovery\ rate\ of\ I(t)\varnothing = 0.43$ [13].

The proportion of infection incidence rate with slow progression to infectious tuberculosis $\theta = 0.5(Assumed)$

Movement rate from $L_F(t)$ *to* $I(t)$ $\gamma = 0.8$ [13]

Movement rate from latent class to Infectious class $\tau = 0.8$ [13].

Tuberculosis induced death rate $\delta = 0.001$ [14].

Recovery rate of $L_f(t)\psi = 0.1$ [14].

The rate of breakdown from slow progressing latent class to fast progressing latent class is indicated in the model by the parameter γ which is the measure of effectiveness of application of anti-retroviral drugs to HIV patients thereby boosting their immune system. We consider three different scenarios (i. e. γ= 0.1, γ = 0.5, and γ = 0.9). The lower the value of γ, the stronger the immune system. The initial population was taken as S(0)=600, $L_s(0)$ = 200, $L_f(0)$ =100 and I(0)= 100.

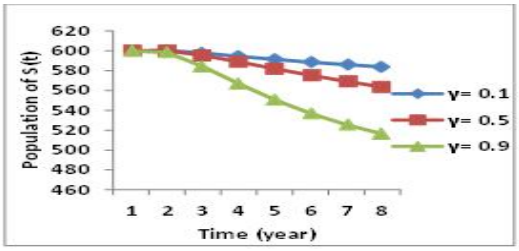


Figure 4.1: **Showing the graphical profiles of the Susceptible class S(t) for γ= 0.1, γ= 0.5 and γ= 0.9.**

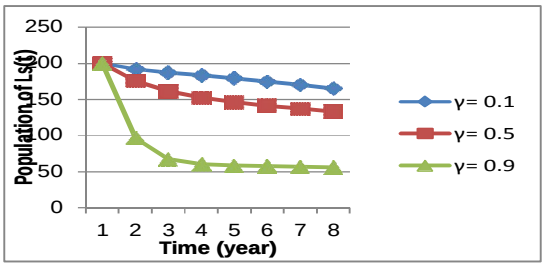


Figure 4.2 Showing the graphical profiles for the slow progressing latent class $L_s(t)$ for γ= 0.1, γ= 0.5 and γ= 0.9

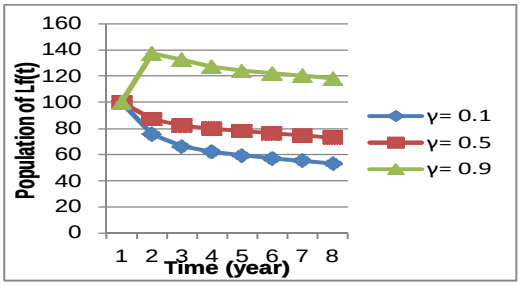


Figure 4.3 Showing the graphical profiles for fast progressing latent class $L_f(t)$ for γ = 0.1, γ = 0.5 and γ=0.9

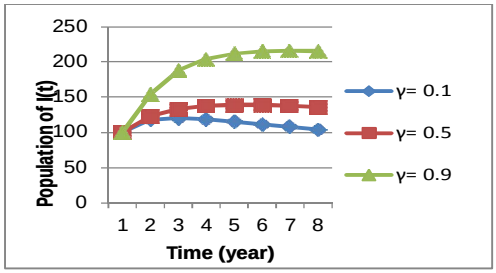


Figure 4.4 Showing the graphical profiles for the infectious class I(t) for γ= 0.1, γ= 0.5 and γ= 0.9

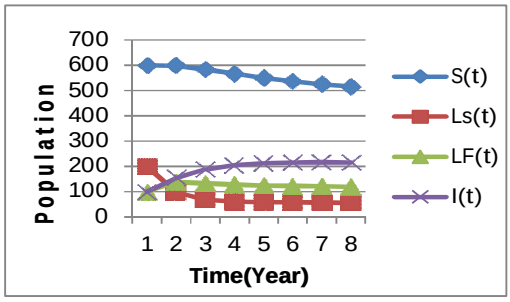


Figure 4.5 Showing the graphical profiles for all the compartment for γ= 0.9

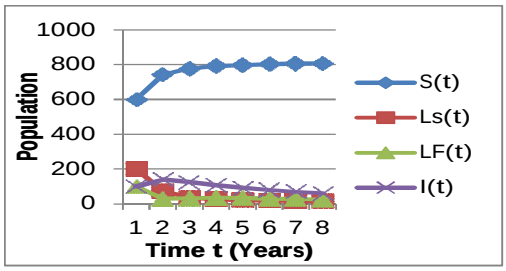


Figure 4.6 Showing the graphical profiles for all the compartment for γ= 0.9, ψ = 0.9 and ε = 0.9

Figure 4.1 shows the graphical profiles for the Susceptible class S(t) for different values of γ. It was observed that the higher the values of γ, the faster the rate at which the Susceptible class decreases. The compartment decreased from the initial 600 to 584, 564 and 516 for γ = 0.1, γ = 0.5 and γ = 0.9 respectively.

Figure 4.2 shows the graphical profiles for the slow progressing latent class L_s (t) for different values of γ. It is observed that this compartment decreased from the initial value of 200 to 165

for γ = 0.1 and 56 for γ = 0.9 .

Figure 4.3 shows the graphical profiles for fast progressing latent class L_f (t) for different values of γ. It was observed that for γ=0.1 this compartment decreases from the initial value of 100 individuals to 53 individuals in seven (7) years and to 73 individuals for γ=0.5. For γ=0.9 which means low immune system, there was initial increase from 100 to 137 after the first year and then decreased gradually to 118 in the 7th year.

Figure 4.4 Shows the graphical profiles for the infectious class I(t) for different values of γ. We observed that when γ=0.1 there was initial increase from 100 to 121 after the second year and thereafter decreases gradually to 101 after seven years. For γ=0.5 this compartment increased gradually to 139 after four years and then decreased gradually to 136 in the seventh year. For γ=0.9 this compartment continue to increase exponentially from initial 100 to 215 in the 7th year.

Figure 4.5 Shows the combination of graphs of all the compartments for γ=0.9
Finally, as a control measure we increased the recovery rate for both Ls(t) and Lf(t) from 0.1 to 0.9 to counter the effect of high γ=0.9 and we observed as shown in fig. 4.6 above that the infection will eventually be eradicated with time.

CONCLUSION

A Mathematical Model on the effects of HIV/AIDS on the progression from Latent Tuberculosis to infectious Tuberculosis was formulated. The system of non-linear differential equations was solved using fourth order Runge-Kutta method and the resulted algorithm was coded using Mapple software. The graphs generated showed that the weaker the immune system the higher the movement rate from latent class to infectious class. This agrees with real life situation since Mycobacterium tuberculosis is prevented from replicating and spreading to other parts of the body by the immune system. Co-infection with HIV weakens the immune system thereby giving the Bacteria ability to replicate and spread to other parts of the body hence progressing from latent stage to infectious state. Effective administration of antiretroviral drugs to HIV patients will decrease the rate of progression from Latent Tuberculosis to Infectious Tuberculosis. However, high Latent TB treatment was also found to eradicate Tuberculosis with time despite the immunosuppressive condition caused by HIV.

RECOMMENDATION

Since tuberculosis is an entirely preventable curable disease, Government should embark on a massive vaccination campaign, the disease treatment guidelines should be strictly adhered to and also increase budgetary allocations for health to reasonable percentage as a means to eradicate the disease.

More centres should be established for antiretroviral drugs administrations to boost the immune system of HIV co infected patients. To be able to eradicate the disease from the population, attention should also be given to latent tuberculosis treatment by administering isoniazid preventive therapy.
This result will serve as a guide for agencies in charge of controlling tuberculosis.

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APPENDIX

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> restart
> with (isah Numerical )
                                        with isah Numerical
>
>
  ρ := 0.045 : μ := 0.014 : β := 0.001 : ϵ := 0.1; ψ := 0.1 : φ := 0.43 :
       θ := 0.5 : γa := 0.1 : τ := 0.8 : δ := 0.001 :
                                                        ϵ := 0.1
>
> k1 := ϵ + γa + μ : k2 := τ + ψ + μ : k3 := φ + μ + δ : h := 1 :
> y1 := 600 : y2 := 200 : y3 := 100 : y4 := 100 :

>
  for i from 1 by 1 to 7 do m11 := h·(ρ − (β·y1 ·y4 ) + (ϵ·y2)
       + (ψ·y3) + (φ·y4) − (μ ·y1 )) ; m12 := h·(β·0·y1·y4 −k1
       ·y2) ; m13 := h·((1 − θ)·β·y1·y4 + γa·y2 − k2 ·y3);

m14 := h·(τ·y3 −k3 ·y4); m21 := h·(ρ − (β·(y1 + m11/2) ·(y4
    + m14/2)) + (ϵ·(y2 + m12/2)) + (ψ·(y3 + m13/2))
    + (φ·(y4 + m14/2)) − (μ ·(y1 + m11/2))); m22 := h
    ·(β·θ·(y1 + m11/2)·(y4 + m14/2) −k1 ·(y2 + m12/2));

m23 := h·((1 − θ)·β·(y1 + m11/2)·(y4 + m14/2)) + γa·(y2
    + m12/2) − k2·(y3 + m13/2)) ; m24 := h·((τ·(y3
    + m13/2)) − k3·(y4 + m14/2)) ; m31 := h·(ρ − (β·(y1
    + m21/2)·(y4 + m24/2)) + (ϵ·(y2 + m22/2)) + (ψ·(y3
    + m23/2)) + (φ·(y4 + m24/2)) − (μ·(y1 + m21/2)));

m32 := h·((β·θ·(y1 + m21/2)·(y4 + m24/2)) − k1·(y2
    + m22/2)); m33 := h·((1 − θ)·β·(y1 + m21/2)·(y4
    + m24/2)) + γa·(y2 + m22/2) − k2·(y3 + m23/2)); m34
    := h·((τ·(y3 + m23/2)) − k3·(y4 + m24/2));

m41 := h·(ρ − (β·(y1 + m31) ·(y4 + m34)) + (ϵ·(y2 + m32))
    + (ψ·(y3 + m33)) + (φ·(y4 + m34)) (μ ·(y1
    + m31))); m42 := h·((β·θ·(y1 + m31)·(y4 + m34)) − k1
    ·(y2 + m32)) ; m43 := h·((1 − θ)·(β·(y1 + m31)·(y4
    + m34)) + γa·(y2 + m32) − k2·(y3 + m33));

m44 := h·((τ·(y3 + m33)) − k3·(y4 + m34)) ; i; y1 := y1 + (1
    /6)·(m11 + 2· m21 + 2· m31 + m41); y2 := y2 + (1/6)
    ·(m12 + 2· m22 + 2· m32 + m42); y3 := y3 + (1/6)·(m13
    + 2· m23 + 2· m33 + m43); y4 := y4 + (1/6)·(m14 + 2
    · m24 + 2· m34 + m44) end do
```