# The MADIM can solve nonlinear ODE systems of biological models with far greater efficiency that classics methods as RK4

## Solving a glioblastoma brain tumor-immune evasion model by multistage Adomian decomposition improved method

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### Introduction

- Glioblastomas are the most common and aggressive tumors of the central nervous system. Glioblastomas are incurable, they must evade the immune response with a mechanism known as "*sneak through*": when the tumor is small the effector cells are unable to recognize it, by the time the immune activation takes place the tumor is too large to be contained [1].

- It is implemented a Multistage Adomian Decomposition Improved Method (MADIM) to find a numerical solution of growth of both Glioblastomas and microglia cells.

### The Glioma-Immune Evasion Model

Dynamics of the immune Cells (microglia):

$$x' = \gamma_1 - \gamma_2 x + \gamma_3 xy, \qquad x(0) = x_0 \tag{1}$$

where:

$x'$ → the growth of the inmune cells.

$\gamma_1$ → the basal generation of microglia.

$\gamma_2$ → the natural death rate of microglia.

$\gamma_3$ → the rate of microglia increase due to inmune/tumor interaction $xy$.

Dynamics of the tumor Cells (gliobastomas):

$$y' = ry\left(1 - \frac{y}{K}\right) - \beta x \frac{y^2}{M^2 + y^2}, \qquad y(0) = y_0 \tag{2}$$

where:

$y'$ → the growth of the tumor cells.

$r$ → the growing rate of logistic model.

$K$ → the saturation constant of logistic model.

$\beta$ → the depredation efficiency.

$M$ → is the half-saturation rate of Holling type III function

| Parameter | Units | Used Value | References |
|---|---|---|---|
| $\gamma_1$ (Basal microglia production) | IC/days | 2500 | [1] |
| $\gamma_2$ (Natural death rate) | 1/days | 0.1 | [4] |
| $\gamma_3$ (Rate of microglia increase) | 1/days | $8.6 \times 10^{-9}$ | [1,2] |
| $x_0$ (Initial inmune cells) | IC | $2.5 \times 10^4$ | [2] |
| $y_0$ (Initial tumoral cells) | TC | $10^2$ | [3] |
| $r$ (Tumor growth rate) | 1/days | 0.18 | [4] |
| $K$ (Saturation threshold) | TC | $10^7$ | [1] |
| $\beta$ (Depredation efficiency) | TC/days*IC | 1 | [4] |
| $M$ (Half-saturation constant) | TC | $7.5 \times 10^4$ | [1,3] |

Table 1: Parameter values used in simulations.

### The Multistage Adomian Decomposition Improved Method (MADIM)

This method is a semi-analytical method for solving ordinary differential equations with initial conditions. Here, we propose a power series solution as a fit of the analytics solution around a neighborhood of a sequence of points, initializing at the initial conditions of the system $a_0 = x(0)$ and $b_0 = y(0)$, then

$$x(t) = \sum_{n=0}^{\infty} \phi_{x,n}(x_0, y_0)\ t^n \quad , \qquad y(t) = \sum_{n=0}^{\infty} \phi_{y,n}(x_0, y_0)\ t^n$$

Solving the systems (1) and (2), the MADIM obtain the sequence of functions

$$\phi_{x,n} = -\frac{1}{n}\left(\gamma_2 a_{n-1} - \gamma_3 \Pi_{n-1}[\vec{x}, \vec{y}]\right)$$

$$\phi_{y,n} = -\frac{1}{n(\delta_1 + b_0^2)}\left(\pi_{n-1}[\vec{y}\,'\vec{y}^{\,2}] - \delta_2 b_{n-1} + \delta_3 \Pi_{n-1}[\vec{y}^{\,2}] - r\Pi_{n-1}[\vec{y}^{\,3}] + \delta_4 \Pi_{n-1}[\vec{y}^{\,4}] + \beta \Pi_{n-1}[\vec{y}^{\,2}\vec{x}]\right)$$

with

$$\delta_1 = M^2,\ \delta_2 = M^2 r\ ,\ \delta_3 = M^2 r/K \text{ and } \delta_4 = r/K.$$

### Results

1. Solution of Glioma-Immune Evasion Model:

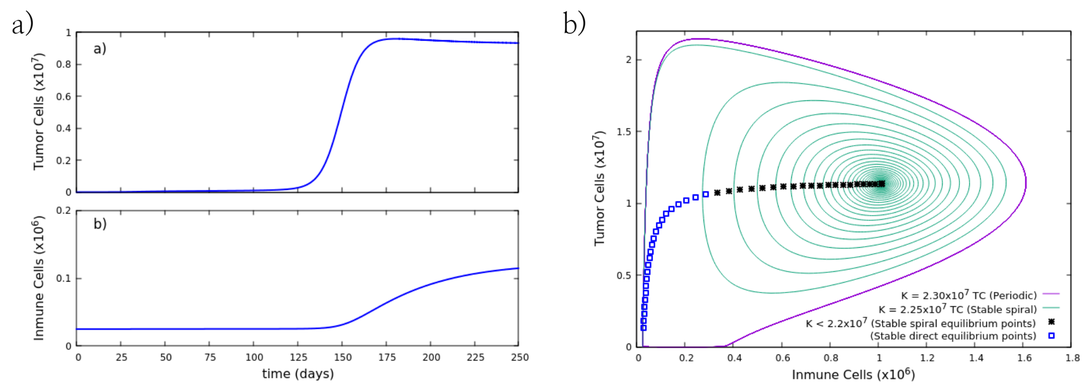


Figure 1. a) Tumor and immure dynamics with real reported parameters (see table 1). b) Phase space of the system (1) and (2) for different values of saturation K

The effect of the "*sneak through*" mechanism is present at the numerical solution of the Glioma-Immune Evasion model using low values of $K$, as is showed at figure 1a. If the tumor growths beyond ($K > 2.3\text{x}10^7$), it is effective the reaction of the of immune cells eliminating the tumor cells (figure 1b).

2. About the numerical method

The MADIM demonstrate a high efficiency performance both at computational cost (figure 2a) and at numerical error (figure 2b), compared with a classical Runge-Kutta 4-order (RK4).

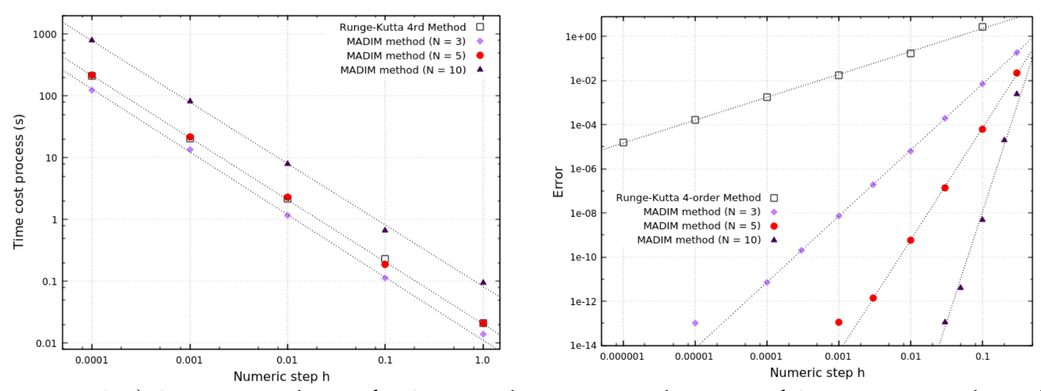


Figure 2. a) Computational cost of MADIM and RK4 measured in terms of CPU resource used time for different time steps. b) Local truncation error of MADIM and RK4 for different time steps.

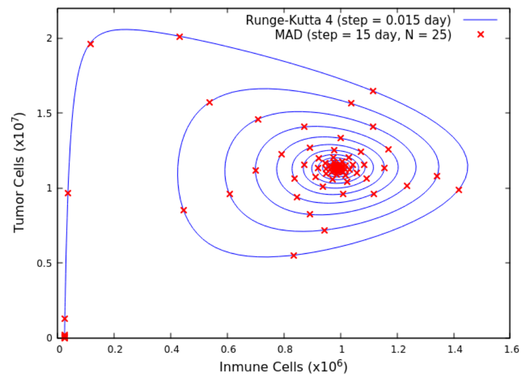


Figure 3. Two Phase path of the system (1) and (2) solved with RK4 (h=0.015) and MADIM (h=15).

The method is so efficient that it allows working out solutions with extremal time steps like h=15 time units (1 unit = 1 day), in contrast to a limited step time required for the RK4, e.g., h=0.015 (see figure 3).

### Conclusions

- The Glioma-Immune Evasion model exhibit the "*sneak through*" mechanism for low values of K and periodic process for values larger ($K > 2.3\text{x}10^7$).

- We prove the MADIM to be a remarkable method for solving nonlinear ODE systems due to their excellent numerical performance.

**References**

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