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Nonsmooth dynamical systems: Application to a cell cycle model

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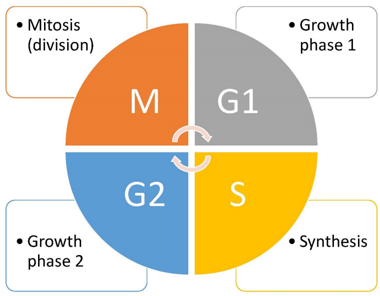

The cycle consisting of repeating growth(Intermediate stages G1, S and G2) and division (Mitosis) is an extremely complex process. Among the key regulators of the cell cycle are Cyclin-Dependent Kinase 1 (CDK1) and the Anaphase-Promoting Complex (APC). We consider a mathematical model of the cell cycle, which is derived in [2] and is based on the dynamics CDK1 and APC. This model considers the cell cycle as a cyclin driven process and is convenient to investigate anti-cancer treatments which block this compound. Denoting the level of activation of CDK1 by x and the level of activation of APC by y and the rate of synthesis of cyclin by α_1 the model is

$$\frac{dx}{dt} = \alpha_1 - \beta_1 x h(n_1, K_1, y) + \alpha_3(1-x)h(n_3, K_3, x), \qquad (1)$$

$$\frac{dy}{dt} = \alpha_2(1-y)h(n_2, K_2, x) - \beta_2 y, \qquad (2)$$

where $h(n, K, z) = \dfrac{z^n}{K^n + z^n}$ is the well known Hill function, a sigmoidal function between 0 and 1. The rest of the constants are easily identified as: β_1 - the natural decay of x when y is at close to its maximum, α_3 - rate of filling existing capacity when x is close to its maximum, etc. Clearly, in this model the Hill function is smoothly switching on and off the terms in which it is involved. One may remark that any switching function can be used and that we can also consider

$$\lim_{n\to\infty} h(n, K, z) = H(z - K),$$

where H is the Heaviside function, that is $H(z) = \begin{cases} 1 \text{ if } z > 0, \\ 0 \text{ if } z < 0. \end{cases}$

We show that by using this discontinuous switch function, it is possible to get a better insight into the possible values of the involved rates and to have a better understanding of the impact of the rate of cyclin synthesis on the cycle period.

The righthand side of (1)-(2) represents a continuous vector field. There is a well developed theory, which among other things includes the Poincare-Bendinxon theorem applied to mathematically prove the existence of a unique limit cycle of (1)-(2). When the Hill function is replaced in (1)-(2) by the Heaviside function, we have a discontinuous righthand side and the model is within the realm of Nonsmooth Dynamical Systems, [3]. The version of the Poincare-Bendixon theorem derived for such systems in [1] is not directly applicable, but we show a direct proof for this case. Overall, the talk promotes the idea that modelling should be guided by biological insight and not be restricted by known or popular mathematical theory.

Keywords: cell cycle, reducing cancer growth rate, nonsmooth dynamical systems

References

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