Dynamic and bifurcation analysis in the p53 network associated with MCF-7 facing radiotherapy

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The tumor suppressor protein p53 plays a central role in orchestrating the cellular response to genotoxic damage, such as the ionizing radiation used in radiotherapy. It activates compensatory mechanisms that include various cellular decision processes such as DNA repair, senescence, or apoptosis, depending on the severity of DNA damage, thereby preventing tumor formation [1, 2, 6]. However, mutations in p53 are found in approximately 50% of human tumors, correlating with poor clinical prognosis due to genomic instability and homeostatic dysregulation. These alterations lead to an overexpression of negative regulators such as MDM2 (a ubiquitin ligase that degrades p53) and WIP1 (a phosphatase that inactivates p53) [1, 2]. In oncology, the MCF-7 cell line represents a model similar to a common type of breast cancer, containing native (wild-type) p53, but the cells do not exhibit apoptosis in response to genotoxic damage, mainly due to the overexpression of MDM2, which inhibits p53 and promotes cell proliferation [3, 4].

Using an *in-silico* model of ordinary differential equations (ODEs), where the system oscillates between cellular decisions, it is possible to propose new therapeutic approaches that direct cells toward a desired response, such as apoptosis [8, 10]. In this work, we developed a mathematical model using ODEs that simulate the p53 molecular network in MCF-7 cells and analyzed the dynamics and their bifurcation points under radiotherapy [7, 8, 9]. We evaluated the dynamic behavior under different radiation doses and the system's responses to variations of ±80% in the synthesis rates of MDM2 and WIP1, in relation to the apoptosis indicator (caspase-3) and its direct influence on p53 [7, 8, 9].

These biological systems exhibit nonlinearity in their dynamic behavior, attributed to system crosstalk, resulting in the caspase trigger time as an indicator of apoptosis depending on the dose for healthy mammary cells, i.e., at a dose of 3 Gy it occurs at ~43 hours, shortening to ~36 hours at 4 Gy and ~33 hours at 5 Gy [6]. In contrast, MCF-7 cells exhibit resistance due to MDM2 dysregulation, regardless of the dose used [3, 4]. Bifurcation analysis at 3 Gy revealed that modifying the WIP1 synthesis rate to less than one-third of its nominal value (>0.03 μM/min) sensitizes MCF-7 cells, triggering apoptotic processes at 20–60 hours [8, 9].

However, variations in the MDM2 synthesis rate do not sensitize cells. It is proposed that this may occur due to failures in degradation mechanisms, perpetuating p53 blockades and inhibiting apoptosis [3, 8, 10, 11]. This study concludes that modulating WIP1 concentration alters the dynamics of the system, promoting apoptosis, positioning WIP1 as a promising therapeutic target for p53 wild-type carcinomas with MDM2 accumulation, such as breast cancer [2, 3, 5, 11].

Keywords: p53, Dynamics, Bifurcation, MCF-7, Radiotherapy, Cell Sensitization.

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