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Mini-review

# Application of mathematical models to metronomic chemotherapy: What can be inferred from minimal parameterized models?

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ABSTRACT

Metronomic chemotherapy refers to the frequent administration of chemotherapy at relatively low, minimally toxic doses without prolonged treatment interruptions. Different from conventional or maximum-tolerated-dose chemotherapy which aims at an eradication of all malignant cells, in a metronomic dosing the goal often lies in the long-term management of the disease when eradication proves elusive. Mathematical modeling and subsequent analysis (theoretical as well as numerical) have become an increasingly more valuable tool (in silico) both for determining conditions under which specific treatment strategies should be preferred and for numerically optimizing treatment regimens. While elaborate, computationally-driven patient specific schemes that would optimize the timing and drug dose levels are still a part of the future, such procedures may become instrumental in making chemotherapy effective in situations where it currently fails. Ideally, mathematical modeling and analysis will develop into an additional decision making tool in the complicated process that is the determination of efficient chemotherapy regimens. In this article, we review some of the results that have been obtained about metronomic chemotherapy from mathematical models and what they infer about the structure of optimal treatment regimens.



## Introduction

The question how anti-cancer chemotherapies should be administered in order to maximize their potential effects and at the same time be safe for the patient is a fundamental one, but also one very difficult to answer conclusively (e.g., see [7,8,30,31,41,47,90,102]). To this day it still eludes clear quantitative answers. Historically, the administration of cancer chemotherapy for a long time has followed established principles based on dose intensity and dose effect which go back to the fundamental work of Skipper [91–93]. In these traditional therapy protocols, cytotoxic agents are administered at maximum tolerated doses (MTD) to counteract disease progression and to kill as many cancer cells as possible. Because of the high toxicities of some of these drugs, it becomes necessary to make prolonged treatment breaks so that the body can recover from treatment induced toxicity. However, in some cases these approaches simply fail with time and the culprit often lies with drug resistance. Cancer cells are genetically unstable and when this gets coupled with high proliferation rates, another main characteristic of many malignant cancers, this leads to significantly higher mutation rates than in healthy cells [32–34]. In addition, growing tumors often exhibit considerable evolutionary ability to enhance cell survival in an environment that is becoming hostile [30]. Modern oncology therefore takes the point of view of a tumor as an agglomeration of sub-populations of cancerous cells of varying therapeutic sensitivities embedded into its microenvironment. This consists of the tumor vasculature, tumor immune system interactions, and many more structures (e.g., fibroblasts and the extra cellular matrix, …), all embedded into healthy tissue.

If specific aspects of tumor development are isolated, clear and simple answers about the structure of optimal chemotherapy protocols can be given. For example, if a homogenous tumor population of chemotherapeutically sensitive cells is assumed—this essentially was the set-up for Skipper's research—and other aspects of the tumor microenvironment are ignored, then mathematical models confirm an MTD strategy: optimal strategies alternate time intervals where chemotherapy is given at maximum

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doses with rest-periods [56,96,98]. But as tumor heterogeneity is included in the modeling, the picture becomes blurry. The Norton-Simon hypothesis [75,76,90] postulates that tumors typically consist of faster growing cells that are sensitive to chemotherapy and slower growing populations of cells that have lower sensitivities or are resistant to the chemotherapeutic agent. An explanation for this feature may lie in the fact that clones achieve resistance through pathways that use up more energy which thus cannot be used for proliferation. While a higher proportion of sensitive cells implies that the majority of cells can be killed, this may turn into a disadvantage when therapy is administered in an unsuitable way. It is conceivable that the killing of all the faster growing sensitive cells enables the resistant population to thrive (which may take years to materialize) while this subpopulation was in some sense previously restrained by the faster growing sensitive populations [31]. It is important to note that such behavior is a basic systems-type mechanism that is equally present for traditional cancer drugs that widely attack all strongly proliferating cells and for targeted therapies. The application of high dose chemotherapy therefore may simply promote the selection of resistant strains through the annihilation of sensitive ones and this eventually makes therapy ineffective. Alternative types of protocols, such as adaptive or metronomic strategies [30,70,84] may give a better outcome or may even be able to control a resistant tumor.

These features become more prevalent when the complex interactions of a tumor with its microenvironment are taken into account as well. There exist experimental and clinical studies which attest that "more is not necessarily better" and it was in this context that the concept of metronomic chemotherapy was introduced in 2000 (e.g., see [16,17,41,50,86]). Metronomic chemotherapy is the frequent administration of chemotherapy at relatively low, non-toxic doses without prolonged treatment interruptions [5,8]. There exists mounting medical evidence that low-dose chemotherapy, while still having a moderate cytotoxic effect on cancerous cells in the absence of significant negative side effects, has anti-angiogenic and immune stimulatory effects (e.g., see [43] for a comprehensive summary of the medical literature on this topic). The hope is that it is possible to give chemotherapy over prolonged time intervals so that, because of the greatly extended time horizon, the overall effect may be improved when compared with repeated short MTD doses: "concentration $\times$ time" matters [47,102]. Furthermore, while low dose chemotherapy seems to have an immune stimulatory effect, high dose chemotherapy simply suppresses the immune system as well taking out another factor that could be utilized in fighting the tumor. Higher doses thus may not only be much more harmful to the healthy cells, but they may also adversely effect the immune system which otherwise might have come to the assistance in combating the tumor.

As a whole, however, and with a few notable exceptions for specific cancers, the ultimate question—how to optimize the anti-tumor, anti-angiogenic and pro-immune effects of chemotherapy by modulating dose and administration schedule—to this date has no conclusive answer. It is here that mathematical modeling and analysis (in silico) can be useful by providing a framework for cancer progression and its response to various treatment options [1]. When is an MTD strategy the better alternative? In which situations can a protracted administration of agents at significantly lower dose rates (the same total dose, but spread in time) achieve better effects? etc. etc. In this article, we review some results that can be drawn about the structure of chemotherapy regimens from mathematical models. Indeed, as increasingly more aspects of the tumor microenvironment are incorporated into the model, optimal solutions tend to favor administration of agents at lower dose rates over MTD strategies.

Due to the inherent restrictions on a mini-review, we limit our discussions to *minimal parameterized deterministic models*. Such models forgo modeling accuracy for the benefit of tractability, but still can lead to robust qualitative conclusions about the structure of optimal solutions that strongly correlate with many approaches taken in medical practice. For example, kinetic parameters are rarely fixed, but vary in time. Keeping them constant is a quite reasonable first approximation if the range of variation is small, but, naturally, incorporating an improved understanding of particular effects may provide a better deterministic modeling of processes while bringing in ideas from mathematical physics leads to stochastic models. Yet, if the implications which solutions have on the biomedical aspects are the same, we generally prefer the simplest possible model. Of course, this is in no way meant to question the great importance of more accurate models (e.g., see [10]). We refer the interested reader, for example, to the paper [82] in which the interplay of parametric variations are analyzed under stochastic fluctuations also with regard to the beneficial aspects of metronomic chemotherapies.

## Metronomic chemotherapy and tumor heterogeneity

The history of mathematical modeling of cancer treatments is long going back to the 1970s and 1980s (e.g., see [21,96,98,99,103]), has been an active area ever since (e.g., [19,26–28,44,66]), and activities only have intensified recently as is attested by a wealth of recent references such as, for example, [4,22]. While periodic chemotherapy schedules were investigated as early as 1985 by Dibrov et al. [20] and by Agur et al. [2] in connection with phase specific drugs, in these early papers it was an implicit assumption that the tumor consists of a homogeneous population of chemotherapeutically sensitive cells. The reality, however, is that tumors often are agglomerations of diverse subpopulations of cells with widely varying phenotypes and chemotherapeutic sensitivities. This has significant implications on the long-term structure of optimal regimes. For many mathematical models optimal solutions then favor a metronomic administration of drugs. The models we discuss below are simplified in the sense that they only consider what could be called pre-existing drug resistance and they do not incorporate processes which model how drug resistance is induced by drug application (e.g., Foo et al. in [24,25] or Perez-Velazquez et al. [85]).

### *Chemotherapy in the presence of sensitive and resistant clones*

A first mathematical model in which the argument for the superiority of metronomic dosing schemes was made was formulated and analyzed by Hahnfeldt, Folkman and Hlatky in 2002 [39]. The dynamical equations describe a standard 2-compartment approach distinguishing two subpopulations of chemotherapeutically sensitive cells, for simplicity termed 'sensitive' (S) and 'resistant' (R). However, it is only assumed that the chemotherapeutic agent has a lower effect (not necessarily none) on the resistant than on the sensitive cells. Transitions between the compartments are allowed, i.e., sensitive cells may mutate into resistant ones, but resistant ones also may resensitize and this is an important feature of the model. This fact is well-documented in the literature on cancer as acquired drug resistance can be lost in a drug free environment (e.g., see [37,42]) whereas naturally such transitions are less likely or do not occur in case of intrinsic drug resistance. In [39], optimizing the maximum asymptotic factor reduction in tumor size between periods in an infinite cycle of periodic therapy periods, the authors come to the conclusion that a regularly spaced metronomic dosing of drugs provides a better long-term suppression of cancer cells when compared with up-front dosing or more irregularly