“Noisy Oncology”: Some Caveats in using Gaussian Noise in Mathematical Models of Chemotherapy

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Abstract. This article discusses some paradoxical results that arise when modelling uncertainties in models of anti-tumor chemotherapies using Gaussian noise. The effects of intrinsic and environmental perturbations and uncertainties on the dynamics of tumor growth and anti-tumor chemotherapy delivered via continuous infusion are considered.

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1. Introduction

Initially, the growth of a tumor is dominated by uncontrolled mythosis [1], which is a phase of exponential growth. Then as the size of the tumor increases, the nutrients available become insufficient to satisfy all of the cells, so they must compete for nutrients and the tumor growth is no longer exponential but tends to plateau — i.e., the growth curve approaches a horizontal asymptote. In practice, only an in vitro tumor nears this final steady state, since in vivo the host (e.g., a human patient) unfortunately dies well beforehand. Many mathematical models of tumor growth involve an ordinary differential equation of form

\[ x' = f(x)x, \]

where \( x(t) \) is the biomass of the tumor and the prime denotes differentiation with respect to the time \( t \), the function \( f(x) \) is approximately constant for small \( x \), and then has derivative \( f'(x) < 0 \) for larger \( x \) until \( x = \hat{x} > 0 \) (say), when the growth stops (i.e., \( f(\hat{x}) = 0 \)). One of the most prominent and robust of this family of models is the generalised logistic equation, where

\[ f(x) = q - rx^\nu, \nu > 0. \]
After diagnosis, patients may undergo various therapies, including surgery as a leading option. However, it cannot be guaranteed that a tumor has been totally removed, and in order to kill metastases the patient may undergo chemotherapy. In some cases, a chemotherapy is carried out beforehand, to reduce the size of the tumor prior to its surgical removal. An anti-tumor chemotherapy may be modelled by the ordinary differential equation

\[ x' = x(q - rx^\nu) - g(t)x, \]

where \( g(t) > 0 \) is the profile of the drug concentration. One way to deliver the therapy is continuous infusion of the drug, in order to partially reduce drug-related major side effects — i.e., \( g(t) \) is approximately constant, so the chemotherapy model becomes

\[
\begin{align*}
x' &= qx - rx^{1+\nu} - cx, \\
x(0) &= x_0 > 0.
\end{align*}
\] (1.1)

Let us suppose that the chemotherapy proceeds for a very long time, so that we are interested in the asymptotic solution behaviour.

The constancy of \( g(t) \) is of course only approximate in reality, and a classical way to represent the variability of \( g(t) \) is to include a white noise perturbation function \( \xi(t) \) of known standard error \( \sigma \). This is considered in § 2, where \( \sigma \) is treated as a stochastic bifurcation parameter. However, in § 3 some potential problems with imposing a Gaussian perturbation in tumor models are stressed, which therefore must be complemented by some biological caveats. Some alternative ways to model uncertainties in mathematical oncology are discussed in the concluding remarks.

2. Deterministic and stochastic modelling of anti-tumor chemotherapy delivered with continuous infusion

It is easy to verify that the deterministic model (1.1) has the following properties:

- if \( 0 \leq c < q \), then \( x(t) \to x_e(c) = ((q - c)/r)^{1/\nu} \), so the tumor is not eradicated; and
- if \( c \geq q \), then \( x' \leq -rx^{1+\nu} \Rightarrow x(t) \to 0^+ \), so the tumor is eradicated.

However, it is important to stress that \( x_e(c) \) is not normally compatible with actual human life experience (even when \( x_e(c) \) is quite small), because of the insurgency of tumor-correlated phenomena — principally tumor diffusion processes that lead to the birth of metastases.

To model the unknown variations of the therapy infusion and also the basic tumor growth rate \( q \), let us include a stochastic term \( \sigma \xi(t)x \) in the model (1.1) to obtain

\[
\begin{align*}
x' &= qx - rx^{1+\nu} - cx + \sigma \xi(t)x, \\
x(0) &= x_0.
\end{align*}
\]