Reviewer's report

Title: Cell Killing and Resistance in Pre-Operative Breast Cancer Chemotherapy

Version: 1 Date: 14 January 2008

Reviewer: Zeljko Bajzer

Reviewer's report:

The authors of this paper have previously proposed mathematical models for assessment and characterization of the effects of breast cancer chemotherapy. Their approach is to develop models which are as much as possible directly related to variety of measured data, and therefore likely useful in clinical decisions. In this paper they present a model which is more comprehensive than previous models---it includes the interplay of cell cycling, cell quiescence and loss, and resistance to therapy. Although there are somewhat similar models in the literature, this new model appears to be more complete, and in the same time relatively simple in terms of numerical calculations. This is in part achieved by using difference equations, rather than differential equations. The manuscript is well written, the results are interesting and well presented, and the discussion is relevant. From my vantage point, the major concern is the mathematical model itself, because its derivation is unclear.

* Major compulsory revisions:

1. In the text and in Fig. 1 it is stated that the proliferating cell population involves age distribution. This is not clear from the equation for $N_p(t)$ in Appendix 1. When the age distribution is involved a cell population is usually described by the function of two variables: age and time. This does not seem to be the case for the equation for $N_p(t)$. Furthermore, the authors stated that their equations are based on equations described by Bertuzzi et al. (Ref. 2), which indeed take into account age and time. It is not clear how the equations presented by the authors are derived from those in Ref. 2. Therefore, it would be necessary to present more details on derivation of equations for $N_p(t)$ and $N_q(t)$, and to explain how is the age of proliferating cells involved. The general structure of these equations can be readily understood from Fig. 1. However, it is not clear how the expressions for $z$ and $u$ were obtained. It should be evident to the reader that the model is justifiable based on reasonable assumptions. In the final analysis all the results presented depend on the acceptability of the model.

2. On page 6 (last paragraph) nine independent model parameters are identified. There is no comment on parameters $\mu$ and $\theta$ which are also included in model equations.

3. The maximum likelihood fitting is performed by using model predictions for patients tumor growth curves (p. 7, 2nd paragraph). The maximum likelihood approach is fully defined when the error distribution in data is specified. Thus, for Gaussian distribution the maximum likelihood fitting is usually reduced to
weighted least-squares method. If the authors used least-squares method, this should be explicitly stated. If something else was used this should be explained in more detail.

* Minor essential revisions:

1. p. 5 â## there is no unit for detection limit.
2. p. 4 (2nd paragraph) â## â#ï an essential feature in the new model is the equilibrium at diagnosis of quiescence, proliferation and natural cell lossâ#ïâ##
The phrase â##at diagnosis of quiescenceâ## seems odd here â## its meaning is not clear to me. This sentence should be revised.
3. p. 7 , the end of the first paragraph: in â##k,<1: â## comma should be deleted.

* Discretionary revisions:

1. p. 3, 1st paragraph. The authors may refer to some literature in regard to models on macroscopic level that consider tumor growth in vivo.
2. p. 4. The authors may introduce some references (at least recent) in which tumor growth models that explicitly take into account subpopulations of quiescent and proliferating cells are proposed.
3. In all equations the authors use â##xâ## for multiplication. This is quite cumbersome. They may rather use the dot in the center.
4. A sentence or two, why the difference equations where used, and how are they justified would be appropriate.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.