Reviewer’s report

Title: On integrative cancer biology approaches to therapeutic gain

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Reviewer: William Hazelton

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General

The authors attempt to formulate two approaches in which control theory could be used to improve cancer treatment. The two strategies consist of a direct approach with preferential killing of cancer cells for cases that are deemed curable, and an indirect approach where non-curable cases are modulated in an attempt to influence non-curable cancer cells to approach the status of curable cancer cells. The authors discuss the approach in terms of childhood pro-B cell leukemia for which DNA microarray data can be used to classify cancers as curable or non-curable. The direct approach is discussed in terms of cell killing with enhanced radiosensitivity through incorporation of iodinated uridine. Control theory is proposed as a regulatory tool to enhance differential killing of malignant cells in mismatch repair (MMR) deficient cancers, where the removal of iodinated uridine is slowed in MMR deficient compared with normal cells.

The readability of the manuscript is improved over the past submission with some of the jargon and generalities removed, but serious difficulties remain. Presenting an actual application of control theory to the problem of childhood leukemia would help cut through the jargon and make this an interesting paper, but otherwise it comes across as not containing too much of real importance.

There are two significant concerns I have. First, an attempt to generalize from childhood leukemia to all cancers leads to a number of implicit assumptions that are not generally warranted. Many assumptions made, which may apply to childhood pro-B cell leukemia, are not generalizable to other cancers. Second, the alternatives for control that are suggested may be not the best choices, or may even be counterproductive.

The paper assumes division of cancers into curable and non-curable status, and knowledge of a cause of the cancer (mis-match repair deficiency in the childhood leukemia example). However, there is no test for most cancers that distinguishes curable and non-curable types. Most cancers do not have a single critical step or cause, but multiple alternative pathways may be disrupted. Tumors are generally not homogeneous - a great diversity of mutations in different cells of a single tumor sample may be caused by
genetic instability that makes it inherently difficult to provide a definite link to any one mutated gene, even if one could afford to do the genetic testing in other than a research setting.

Other assumptions in this paper don't generally hold true. The assumption that a cell killing approach (the direct approach) is useful for curable but not non-curable cancers is not without question - survival is often extended for non-curable cancers using cell killing. We often can't make the distinction between curable and non-curable until after the fact. The assumption that a comparison of killing of malignant cells compared to normal cells is a good target for control is flawed - what may matter as much or more is the differential re-growth of the cancer and normal cells following depletion of cells, through homeostatic regulation of the organ. For example, there may be efficient killing of cancer cells and some normal cells, but if the cancer cells repopulate the organ much more efficiently, then the treatment may be detrimental to long term survival even if it kills lots of malignant cells. Thus, long term survival is generally a more important metric to use for all cancer types.

The assumption of the indirect approach that regulating "non-curable" cancer cells to achieve the behavior of "curable" cancer cells may be counter productive. Killing of cancer cells is often achieved as they divide, thus they may be more "curable" if they divide constantly. However, making a slowly dividing "non-curable" cell look like a curable cell through regulation that has the effect of making it divide more rapidly would make it more lethal if it remained inherently difficult to kill. The measure of efficacy of an intervention should be purely on survival of the individual. A control effort to make the non-curable cancer cells look curable would appear to be more a diversion or masking of the problem and waste of resources, and certainly complicate further followup and prognostic decision making.

An alternative strategy for intervention that was not discussed is almost opposite to making the non-curable cells look like curable cells. That would be to try to drive them to have further differences that would improve recognition and targeting.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Given the assumptions in this paper, it might be better for the authors to focus the article on childhood leukemia and work on actually applying control theory to the example they propose. The paper would certainly carry more interest if a serious effort were made to acquire sufficient data to attempt application of control theory to that problem.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
**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

**Declaration of competing interests:**

I declare that I have no competing interests.