Author's response to reviews

Title: On systems and control approaches to therapeutic gain

Authors:
- Tomas Radivoyevitch (radivot@hal.cwru.edu)
- Kenneth A Loparo (kal4@case.edu)
- Robert C Jackson (bjackson@cyclacel.com)
- W DAVID Sedwick (wds@case.edu)

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Author's response to reviews: see over
Dear BMC Cancer Editor,

Changes made to MS: 5184938277240547 entitled “On systems and control approaches to therapeutic gain” are described point-by-point below.

Thank you,
Tom Radivoyevitch

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Response to Referee 1:

Point-by-point responses follow

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,

1) The direct approach does not specify that cases must be 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. 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,

3) Agreed. This is a lot to ask, however, as it requires a validated process model.

but otherwise it comes across as not containing too much of real importance

4) One value of the paper is that it helps us ask the right questions.

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.

5) At no point did we ever claim applications to all cancers. If the framework has something to say about 1% of all cancers, that would be enough for us.

Second, the alternatives for control that are suggested may be not the best choices, or may even be counterproductive.

6) Please keep in mind that this is very pre-clinical and that we have to start somewhere.

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).

7) Again, we’re only going after those cancers for which these conditions are true.

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 by 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.
8) Agreed. This is why we make no attempt to go after all cancers.

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.

9) We never made this claim. Further, we are conscious of the fact that MMR deficiency often arises as a secondary drug resistance event and that if such a clone is life limiting for a patient, that the direct approach might be applicable. Indeed, this is what we were alluding to in the first paragraph in the discussion.

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.

10) Tissue level models are needed but are outside the scope of this paper. Further, long term survival is not readily modeled mechanistically.

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.

11) Indeed, we do favor the direct approach, see the last paragraph in the Discussion.

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.

12) Not so, this was indeed discussed in the Discussion where we stated that “Indeed, one can argue that instead of annihilating differences between malignant and normal cells, we should seek to exaggerate them. In other words, in the case of BCR-ABL leukemia, we should look for ways to increase the tyrosine kinase activity of bcr-abl even further, rather than annihilate it as in the indirect approach. Conceptually, our Case ICBP is pursuing this strategy for mismatch repair deficient cancers where one of our goals is to exaggerate DNA repair system differences between MMR- malignant and normal cells by inhibiting base excision repair (BER) using methoxyamine [35]; the rationale is that MMR- cells are more dependent on BER than their normal counterparts, so total repair
capacity differences between normal and MMR- malignant counterpart cells should increase with BER inhibition. This paragraph has been upgraded.

Sincerely,
Tom Radivoyevitch

Response to Referee 2

Thank you for your recommendation to look for ways to increase the clarity of the writing further.

Thank you,
Tom Radivoyevitch