S4 Text

Range sensitivity analysis

1. Method

The range sensitivity measures (SM) defined here are similar to the local sensitivity measures of the main manuscript; however, the inputs are now varied over the anticipated value range [1, 2], instead of assuming a small perturbation around the baseline values. Each input parameter takes its minimum and maximum value and the corresponding change in the calculated CKR, expressed as a percentage of the reference value, is recorded. The rest of the model parameters are kept at their baseline values. All percentage changes in the output are then expressed in relation to ±1% variation of the input, by dividing with the percentage change of the input, according to the formulas:

\[ SM_{\text{max}} = \frac{(CKR_{\text{max}} - CKR_{\text{base}})}{(p_{i,\text{max}} - p_{i,\text{base}})/p_{i,\text{base}}} \]  

\[ SM_{\text{min}} = \frac{(CKR_{\text{min}} - CKR_{\text{base}})}{(p_{i,\text{min}} - p_{i,\text{base}})/p_{i,\text{base}}} \]  

\[ SM_{\text{range}} = \frac{SM_{\text{max}} - SM_{\text{min}}}{2} \]  

where \( p_{i,\text{base}} \): the baseline value of the \( i \)-th parameter, \( p_{i,\text{max}} \): the maximum value of the \( i \)-th parameter, \( p_{i,\text{min}} \): the minimum value of the \( i \)-th parameter, \( CKR_{\text{base}} \): the calculated CKR with all parameters set at their baseline values, \( CKR_{\text{max}} \): the calculated CKR with the \( i \)-th parameter, only, set at its maximum value, \( CKR_{\text{min}} \): the calculated CKR with the \( i \)-th parameter, only, set at its minimum value.

The value range of input parameters (Table A) has been derived after taking into consideration the literature (Table 4 of main manuscript), while certain cell proliferation constraints should be satisfied (e.g. positive growth rate, volume doubling time higher than 26 days, percentage of stem cells not exceeding 1%). It should be noted that between the adenocarcinoma (ADC) and squamous cell carcinoma (SCC) different value ranges for some of the parameter are observed (Table A). These boundaries have been derived after applying the aforementioned constraints, and their values depend on the baseline values of the remaining model parameters [3, S2 Text].

2. Results

The range sensitivity measures consider a larger increment compared with their local counterparts and, therefore, are expected to give a different value for parameters having a non-linear effect on the output. In our case, a small deviation from linearity exists for the majority of the input parameters (Fig 3 of manuscript). As a result, a very small divergence between the values of the local and range sensitivity measures is noted (Table B). Looking at the overall sensitivity
In Silico Oncology: Quantification of the In Vivo Antitumor Efficacy of Cisplatin-Based Doublet Therapy in Non-Small Cell Lung Cancer (NSCLC) through a Multiscale Mechanistic Model

Eleni Kolokotroni, Dimitra Dionysiou, Christian Veith, Yoo-Jin Kim, Jörg Sahczynski, Astrid Franz, Aleksandar Grjic, Jan Palm, Rainer M. Bohle, Georgios Stamatakos

(two last columns of Table B), the most remarkable differences are observed for the following parameters:

- \( T_C, T_{C, \text{stem}}, T_{C, \text{LIMP}} \): A considerable deviation between the results of the local and the range methods is observed for the SCC case, with the latter method indicating a higher overall sensitivity. For the ADC case a noteworthy deviation exists only when the cell cycle duration of both stem and LIMP cells are varied at once, i.e. for \( T_C \).
- \( R_{\text{ADiff}} \): The range method gives a higher overall sensitivity for the ADC case. However a low sensitivity is still indicated by both methods.
- \( N_{\text{LIMP}} \): The range method gives a slightly higher overall sensitivity especially for the SCC case. However, a low sensitivity is still indicated by both methods.
- \( P_{\text{G0toG1}}, P_{\text{G0toG1,stem}} \): The range method gives a fairly lower overall sensitivity especially for the ADC case. However, a relatively high sensitivity is indicated by all methods.

Both methods identify the same parameters having a trivial effect on output (overall sensitivity measure <0.1% in Table C). The only noteworthy deviation concerns the parameter \( R_{\text{ADiff}} \), as stated above. The local method ranks the parameter as non-sensitive for both the ADC and SCC cases, whereas the range method indicates a low sensitivity for ADC only (Table B).

For the rest of the parameters, having a low to high impact on output (overall sensitivity measure >0.1% in Table C), the local method results almost in the same ranking as the range one. Both methods identify the same parameters as the two most sensitive. Differences observed in the overall ranking order are due to the underestimation of the sensitivity for \( T_C \) compared to \( P_{\text{G0toG1}} \) and \( P_{\text{G0toG1,stem}} \) by the local method, resulting in a lower rank in respect to the range method.

In summary, the sensitivity results of the local sensitivity measures are rather consistent with the range ones, even though the latter method encompasses the effect of non-linearity.

**Table A: Input Parameter Values**

| Parameter | ADC representative case | SCC representative case |
|-----------|-------------------------|-------------------------|
| \( T_C \) | 42                      | 60                      |
| \( T_{C, \text{stem}} \) | 42                      | 60                      |
| \( T_{C, \text{LIMP}} \) | 42                      | 60                      |
| \( T_{GR} \) | 382                     | 242                     |
| \( T_{GR, \text{stem}} \) | 382                     | 242                     |
| \( T_{GR, \text{LIMP}} \) | 382                     | 242                     |
| \( T_N \) | 23                      | 7                       |
| \( T_A \) | 4                       | 25                      |
| \( R_A \) | 0.0003                  | 0.00036                 |
| \( R_{\text{ADiff}} \) | 0.008                   | 0.001                   |
| \( R_{\text{NDiff}} \) | 0.0009                  | 0.001                   |
| \( P_{\text{G0toG1}} \) | 0.5                     | 0.1                     |
| \( P_{\text{G0toG1,stem}} \) | 0.5                     | 0.1                     |
| \( P_{\text{G0toG1,LIMP}} \) | 0.5                     | 0.1                     |
| \( N_{\text{LIMP}} \) | 18                      | 22                      |
| \( CKF \) | 0.5                     | 0                       |
| \( P_{\text{sym}} \) | 0.2                     | 0.37                    |
| \( P_{\text{sleep}} \) | 0.265733                | 0.2796                  |
| \( CKR_{\text{G0G1}} \) | 0.2                     | 0.67                    |

\( ^a \) Derived based on the constrain for positive growth rate.
\( ^b \) For \( T_C = 18 \) no solution with the sum of cell kill rates < 1 exists.
\( ^c \) Derived based on the constrain for a volume doubling time higher than 26 days.
\( ^d \) Derived based on the constrain for a fraction of stem cells lower than 0.001.
\( ^e \) No solution for parameter values above the considered upper limit. More specifically, treatment shrinks tumor at a higher extent compared to the observed volume reduction for all values of cisplatin’s cell kill rate.
**In Silico Oncology:** Quantification of the *In Vivo* Antitumor Efficacy of Cisplatin-Based Doublet Therapy in Non-Small Cell Lung Cancer (NSCLC) through a Multiscale Mechanistic Model

Eleni Kolokotroni, Dimitra Dionysiou, Christian Veith, Yoo-Jin Kim, Jörg Sahczynski, Astrid Franz, Aleksandar Grgic, Jan Palm, Rainer M. Bohle, Georgios Stamatakos

---

**Table B: Sensitivity results. Comparison with local sensitivity measures**

| Case          | Parameter | -1% Parameter Variation | +1% Parameter Variation | Overall Variation |
|---------------|-----------|-------------------------|-------------------------|-------------------|
|                | SM<sub>%</sub> | SM<sub>min</sub> | SM<sub>max</sub> | SM<sub>±%/SM</sub> | SM<sub>range</sub> |
| **ADC representative case** | | | | | |
| T<sub>C</sub> | 0.36215 | 0.55016 | -0.20877 | -0.19057 | -0.28546 | -0.37037 |
| T<sub>C,stem</sub> | 0.15179 | 0.16567 | -0.07270 | -0.07594 | -0.11224 | -0.12081 |
| T<sub>C,LIMP</sub> | 0.28096 | 0.32963 | -0.14030 | -0.07492 | -0.21063 | -0.20228 |
| T<sub>g1</sub> | 0.03331 | 0.12818 | -0.04544 | -0.00714 | -0.03938 | -0.06766 |
| T<sub>g1,stem</sub> | 0.12712 | 0.19014 | -0.10131 | -0.08587 | -0.11421 | -0.13801 |
| T<sub>g1,LIMP</sub> | -0.07368 | -0.10114 | 0.08579 | 0.08308 | 0.07973 | 0.092109 |
| T<sub>N</sub> | -0.00093 | 0.00082 | 0.01839 | 0.00368 | 0.00966 | 0.001427 |
| T<sub>A</sub> | 0.00083 | 0.00221 | 0.00508 | 0.00013 | 0.00213 | -0.00104 |
| R<sub>A</sub> | 0.16022 | 0.15489 | -0.17712 | -0.17717 | -0.17317 | -0.16603 |
| R<sub>Diff</sub> | -0.00886 | 0.28591 | 0.00039 | 0.00463 | 0.00646 | 0.01407 |
| R<sub>NDiff</sub> | 0.00499 | -0.00111 | 0.00428 | 0.00300 | -0.00464 | 0.00071 |
| P<sub>GI-G1</sub> | -0.92662 | -0.92061 | 0.80399 | 0.56740 | 0.85849 | 0.74401 |
| P<sub>GI-G1,stem</sub> | -0.86893 | -0.8829 | 0.77345 | 0.56509 | 0.81589 | 0.72400 |
| P<sub>GI-G1,LIMP</sub> | -0.03796 | -0.03497 | 0.04177 | 0.04681 | 0.03987 | 0.04089 |
| N<sub>LIMP</sub> | 0.20374 | 0.28702 | -0.13113 | -0.09726 | -0.16743 | -0.19214 |
| CKF | 0.02495 | 0.03783 | -0.04721 | -0.03718 | -0.03608 | -0.03751 |
| P<sub>sym</sub> | -1.03013 | -1.03483 | 1.03419 | 0.88703 | 1.03216 | 0.96093 |
| P<sub>sleep</sub> | 1.00887 | 1.13015 | -0.98271 | -1.00150 | -0.99579 | -1.06583 |
| CKR<sub>eff</sub>C | -0.07704 | -0.07735 | 0.06311 | 0.06376 | 0.07007 | 0.07055 |
| **SCC representative case** | | | | | |
| T<sub>C</sub> | 0.38847 | 1.45248 | -0.29436 | -0.14327 | -0.34141 | -0.79788 |
| T<sub>C,stem</sub> | 0.19777 | 0.45636 | -0.16914 | -0.09868 | -0.18345 | -0.27752 |
| T<sub>C,LIMP</sub> | 0.17016 | 0.72548 | -0.12011 | -0.03999 | -0.14513 | -0.38274 |
| T<sub>g1</sub> | -0.07892 | -0.07947 | 0.08079 | 0.09267 | 0.07985 | 0.08607 |
| T<sub>g1,stem</sub> | 0.01392 | 0.02635 | -0.03329 | -0.01606 | -0.02361 | -0.02120 |
| T<sub>g1,LIMP</sub> | -0.10506 | -0.10771 | 0.11052 | 0.10377 | 0.10697 | 0.10574 |
| T<sub>N</sub> | -0.00373 | -0.00588 | 0.01612 | 0.00368 | 0.00993 | 0.02138 |
| T<sub>A</sub> | 0.00478 | 0.00158 | 0.00700 | -0.00026 | 0.00111 | -0.00092 |
| R<sub>A</sub> | 0.07715 | 0.06257 | -0.05874 | -0.06823 | -0.06795 | -0.06540 |
| R<sub>Diff</sub> | -0.00884 | -0.00337 | 0.00498 | 0.00741 | 0.00691 | 0.00539 |
| R<sub>NDiff</sub> | -0.00022 | -0.00027 | 0.00667 | 0.00067 | 0.00344 | 0.00047 |
| P<sub>GI-G1</sub> | -0.36875 | -0.40018 | 0.34977 | 0.23344 | 0.36875 | 0.31681 |
| P<sub>GI-G1,stem</sub> | -0.31340 | -0.35189 | 0.30110 | 0.21309 | 0.30725 | 0.28249 |
| P<sub>GI-G1,LIMP</sub> | -0.04049 | -0.04802 | 0.04482 | 0.02115 | 0.04266 | 0.03458 |
| N<sub>LIMP</sub> | 0.15648 | 0.25710 | -0.06639 | -0.07749 | -0.11144 | -0.16730 |
| CKF | 0.02646 | 0.01629 | -0.00694 | -0.01271 | -0.02646 | -0.01450 |
| P<sub>sym</sub> | -2.57337 | -2.61168 | 2.27842 | 1.94370 | 2.42590 | 2.27769 |
| P<sub>sleep</sub> | 2.73239 | 2.37882 | -3.11203 | -3.10590 | -2.92221 | -2.74236 |
| CKR<sub>eff</sub>C | 0.12396 | 0.10765 | -0.14345 | -0.16382 | -0.13370 | -0.13573 |

* SM<sub>%</sub> = (SM<sub>max</sub> - SM<sub>%</sub>) / 2
**In Silico Oncology**: Quantification of the *In Vivo* Antitumor Efficacy of Cisplatin-Based Doublet Therapy in Non-Small Cell Lung Cancer (NSCLC) through a Multiscale Mechanistic Model

Eleni Kolokotroni, Dimitra Dionysiou, Christian Veith, Yoo-Jin Kim, Jörg Sahczyński, Astrid Franz, Aleksandar Grgić, Jan Palm, Rainer M. Bohle, Georgios Stamatakos

**Table C**: Parameter ranking derived based on the overall sensitivity

| Parameter* | Sensitivity‡ | Parameter* | Sensitivity‡ |
|-------------|--------------|-------------|--------------|
| $P_{\text{sleep}}$ | 1.95900 | $P_{\text{sleep}}$ | 1.90410 |
| $P_{\text{sym}}$ | 1.72903 | $P_{\text{sym}}$ | 1.61931 |
| $P_{G0\to G1}$ | 0.61362 | $T_{C}$ | 0.58413 |
| $P_{G0\to G1, stem}$ | 0.56157 | $P_{G0\to G1}$ | 0.53041 |
| $T_{C}$ | 0.31344 | $P_{G0\to G1, stem}$ | 0.50324 |
| $T_{C, \text{LIMP}}$ | 0.17788 | $T_{C, \text{LIMP}}$ | 0.29251 |
| $T_{C, \text{stem}}$ | 0.14785 | $T_{C, \text{stem}}$ | 0.19917 |
| $N_{\text{LIMP}}$ | 0.13944 | $N_{\text{LIMP}}$ | 0.17972 |
| $R_{A}$ | 0.12056 | $R_{A}$ | 0.11572 |
| $\text{CKR}_{\text{dFdC}}$ | 0.10189 | $\text{CKR}_{\text{dFdC}}$ | 0.10314 |
| $T_{G0, \text{LIMP}}$ | 0.09326 | $T_{G0, \text{LIMP}}$ | 0.09892 |
| $T_{G0, \text{stem}}$ | 0.06891 | $T_{G0, \text{stem}}$ | 0.07961 |
| $T_{G0}$ | 0.05962 | $T_{G0}$ | 0.07687 |
| $P_{G0\to G1, \text{LIMP}}$ | 0.04126 | $R_{\text{ADiff}}$ | 0.07323 |
| $\text{CKF}$ | 0.03127 | $P_{G0\to G1, \text{LIMP}}$ | 0.03774 |
| $T_{N}$ | 0.00979 | $\text{CKF}$ | 0.02601 |
| $R_{\text{ADiff}}$ | 0.00577 | $T_{N}$ | 0.0114 |
| $R_{\text{NDiff}}$ | 0.00404 | $T_{A}$ | 0.00098 |
| $T_{A}$ | 0.00162 | $R_{\text{NDiff}}$ | 0.00059 |

* Sorted from high to low sensitivity.
‡ Derived by averaging the absolute of the overall sensitivity measure for ADC and SCC.

**References**

[1] U.S. EPA. TRIM, Total Risk Integrated Methodology, TRIM FaTE Technical Support Document Volume I: Description of Module. Office of Air Quality Planning and Standards. 2002. EPA-453/R-02-011a. Available in http://nepis.epa.gov/Adobe/PDF/2000NRID.PDF (last visited on 1 July 2016)

[2] U.S. EPA. Risk Assessment Guidance for Superfund: Volume III - Part A, Process for Conducting Probabilistic Risk Assessment. 2001. EPA 540-R-02-002. Available in https://www.epa.gov/sites/production/files/2015-09/documents/rags3adt_complete.pdf (last visited on 1 July 2016)

[3] Kolokotroni EA, Dionysiou DD, Uzunoglu NK, Stamatakos GS. Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model. Math Comput Model. 2011;54:1989-2006. doi:10.1016/j.mcm.2011.05.007