**QCIC Model Operation Instructions**

* **QCIC model basic operation code**

**【1】Function description of main program files**

1. The "VirPat.m" file is primarily used for generating virtual patients, where "n" represents the number of virtual patients to be generated, and "number" indicates the number of CPU cores for parallel computing.

（2）The "main.m" file is an internal function required for parallel computing, primarily used to execute the fourth-order Runge-Kutta algorithm and store the virtual patient data in the "VP" folder.

（3）The "QCIC.m" file is primarily used for storing the computational formulas of the model.

（4）The "parameter.m" file stores the parameters for the QCIC model.

（5）The "LHS\_Matrix.m" file is used to generate parameter information related to tumor heterogeneity for virtual patients.

（6）The "initialization\_parameter.m" file and the "initialization.m" file are used to store the initial values for iterative calculations of differential equations.

**【2】Description of the data storage folder**

（1）"VPi.mat" stores the computation results of the i-th virtual patient.

（2）The "VP\_LHS\_Matrix.mat" file describes the tumor heterogeneity parameters of the generated virtual patients.

* **Brief description of the drawing program**

（1）The "Fig.2" folder is used for plotting the comparison of short-term efficacy evaluation indicators at the population level between model simulations and clinical data. The extracted clinical data are nested into the corresponding plotting program. The results of the model simulations are also placed in the plotting program in the form of data points.

（2）The "Fig.3" folder is used to illustrate the evolution of the disease dynamics of 100 baseline patients. The "Fig.3a", "Fig.3b", and "Fig.3c" folders are dedicated to presenting the computational results for the control group, the TAS-102 chemotherapy group, and the combination therapy group of TAS-102 with Bevacizumab, respectively. The "VP" folder contains data for these 100 baseline patients. Due to the large volume of data, it is not convenient to upload here. You can contact the corresponding author to get this part of the data.

（3）The "Fig.4" folder illustrates the comparison of long-term treatment outcomes (M-OS and survival frequency) between model simulations and clinical data. The clinical data extracted from clinical trials are directly saved in the corresponding folder, and the numerical data from model simulations are placed in the plotting program.

（4）The "Fig.5" folder is dedicated to plotting survival curves. The survival curve data extracted from clinical trials are stored in the "Placebo\_Clin" folder. The "Ave.mat" file saves the corresponding model-calculated survival curve values for direct access. The folders "Placebo\_VP", "TAS102\_VP", and "TASBEV\_VP" are used to store data for the 100 baseline patients in the control group, the TAS-102 chemotherapy group, and the TAS-102 combined with Bevacizumab group, respectively. As mentioned earlier, this part of the data can be obtained from the corresponding author.

（5）The "Fig.6" folder is used for plotting the distribution of different predictive biomarkers between responders and non-responders. The folders "Placebo\_VP", "TAS102\_VP", and "TASBEV\_VP" are utilized to store data for 4,000 randomly generated patients in the control group, the TAS-102 chemotherapy group, and the TAS-102 combined with Bevacizumab group, respectively. As mentioned before, this part of the data can be obtained from the corresponding author. Other process programs and calculation results are only saved in their corresponding locations within the "Fig.6" folder.

（6）The "Fig.7" folder is dedicated to plotting the ROC analysis results for different biomarkers. The folders "TAS102\_VP" and "TASBEV\_VP" are used to store 500 valid data points extracted from the 4,000 randomly generated patients in the TAS-102 chemotherapy group and the TAS-102 combined with Bevacizumab group, respectively. Due to the large volume of data, this part of the data can be obtained from the corresponding author.

（7）The "Fig.8" folder is used for plotting survival analysis results based on high and low expression levels of different biomarkers. All process files and plotting programs are stored within the "Fig.8" folder. Similarly, due to the volume of data, the virtual patient data in "TASBEV\_VP" can be obtained from the corresponding author.

（8）The "Fig.S2" folder is used for plotting comparisons between the results of different clinical trials and model predictions. All data are saved in the corresponding plotting programs.

（9）The "Fig.S3" folder is used for plotting the results of the global sensitivity analysis. The "VP" folder is designated for storing the results of 1,000 calculations. This part of the data can be generated by running the relevant programs, or you can contact the corresponding author to obtain the raw data.

（10）The "Fig.S4" folder is used for plotting the global sensitivity analysis results of the 21 tumor heterogeneity parameters required for generating virtual patients.

（11）The "Fig.S5" to "Fig.S10" folders are used for plotting the output results of model variables in the control group, the TAS-102 chemotherapy group, and the TAS-102 combined with Bevacizumab group. The "VP" folder contains the generated virtual patient data, which can be self-generated or obtained from the corresponding author.