Comparison of Sensitivity Analysis Methods in the Context of a QSP Model for Gout

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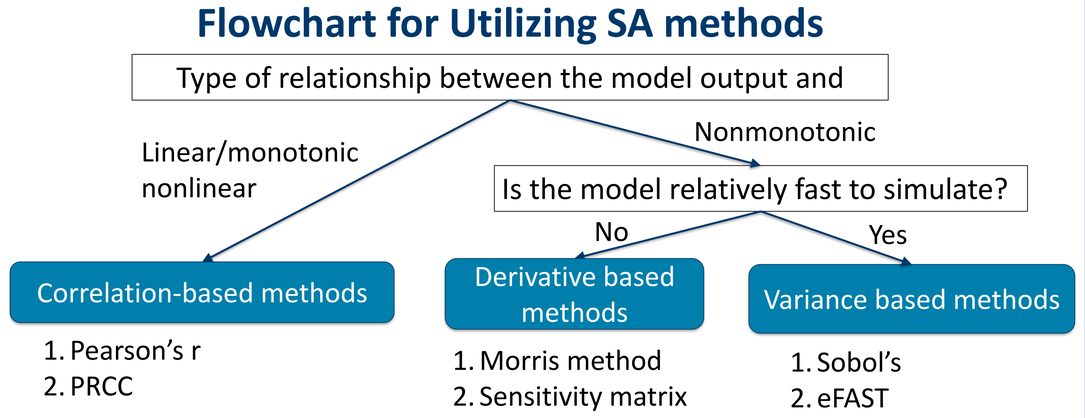
OBJECTIVE

As quantitative systems pharmacology (QSP) models are increasingly used to inform key questions related to drug development, there is need for sensitivity analysis (SA) to inform an understanding of influential model parameters which can improve confidence in predictions [1,2]. Applying SA methods during QSP model development can be difficult due to model size, number of parameters, and nonlinearities. We compare three SA techniques to shed more light on the most influential parameters impacting a model output of interest. By applying these methods to a validated model with known responses, we aim to provide insight for when SA methods are applied to other QSP models.

METHODS

GOUTSYM OVERVIEW DIAGRAM

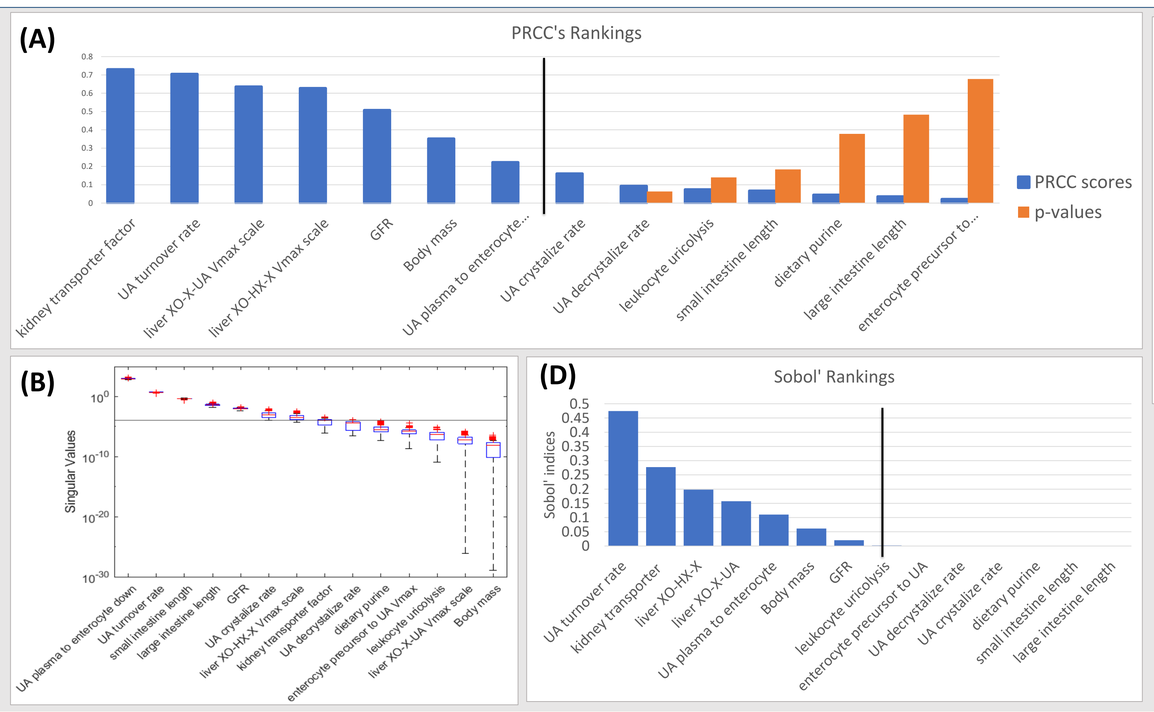
Flowchart for Utilizing SA methods



RESULTS

CUT-OFF THRESHOLD TO DISTINGUISH BETWEEN LESS TO MORE IMPORTANT PARAMETERS AMONG DIFFERENT SA METHODS

- PRCC identified 7 most influential parameters based on their p-values <0.01 (Panel A)
- Sensitivity matrix considered any parameter is significant if its singular value less than 10e-4 (Panel B)
- Morris method requires users to set a limit of variation in the parameters' elementary effect (Panel C)
- Sobol' method requires user to impose their subjective threshold boundary to distinguish between the less and more important parameters; here, we define an important parameters are those who contribute more than 10% of the model variation (Panel D)



THREE OUT OF FOUR SA METHODS SHARING SIMILAR RANKING OF IMPORTANT PARAMETERS

- The top 7 most important parameters are consistent among 3 methods: Sobol' method, PRCC, SA matrix (average norm metric)
- Morris method only identify that there are 4 parameters are most impactful to the model (*), 3 of which coincide with the top 7 important parameters by Sobol' method, PRCC, SA matrix (average norm metric). This could improve by refining the sampling scheme in Morris method
- SA matrix SVD-QR approach identify different set of sensitive parameters than the rest of the methods

COMPARING COMPUTATIONAL EFFICIENCY AMONG VARIOUS SA METHODS

- PRCC and Morris method are the most computationally efficient
- Sobol's method requires the most computing power and model evaluation
- SA matrix approach is the intermediate method that is less efficient than PRCC but not as computationally intensive as Sobol's method

	Sobol' method	PRCC	SA average norm	SA matrix SVD-QR	Morris method
'UA turnover rate'	1	1	2	2	3*
'kidney transporter factor'	2	2	1	8	9
'liver XO-HX-X Vmax scale'	3	4	4	7	1*
'liver XO-X-UA Vmax scale'	4	3	3	13	5
'UA plasma to enterocyte down'	5	7	7	1	6
'Body mass'	6	6	5	14	4*
'GFR'	7	5	6	5	8
'leukocyte uricolysis'	8	11	9	12	2*
'enterocyte precursor to UA Vmax'	9	8	8	11	10
'UA decrystalize rate'	10	14	13	9	13
'UA crystalize rate'	11	10	14	6	14
'dietary purine'	12	9	12	10	12
'small intestine length'	13	13	10	3	11
'large intestine length'	14	12	11	4	7

Cut-off by PRCC and Sobol' method

* *4 most important parameters identified by Morris method*

	PRCC	SA matrix	Sobol's method	Morris Method
Simulation time	5 mins	31 hours	900 hours	5.6 hours
Model evaluation	413†	413+413*14=6195*	200000*	1503

**Sobol's method and SA matrix method are run on a Virtual Machine: Intel(R) Xeon(R) Gold 6326 CPU (32 cores), 128 GB RAM*

† *PRCC simulations are run on a laptop: DELL 11th Gen Intel(R) Core(TM) i7-1185G7 @ 3.00GHz (4 cores), 16.0 GB RAM*

CONCLUSION

Through this case study, we noted that less complex SA methods like PRCC and SA-QR have similar overall rankings to the Sobol' method even in a complex QSP model. Sobol' method requires fewer assumptions to implement but may be infeasible without significant computational resources. Each increase in complexity, from correlation-based to derivative-based to variance-based, provides a tradeoff between computation time versus more flexibility and capability to capture complex model responses. Further investigations could inform generalizability of this case study, but the results herein can help inform the choice of SA method during QSP model development.

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