Quantitative Weight of Evidence Model for Assessing Adverse Outcome Pathways

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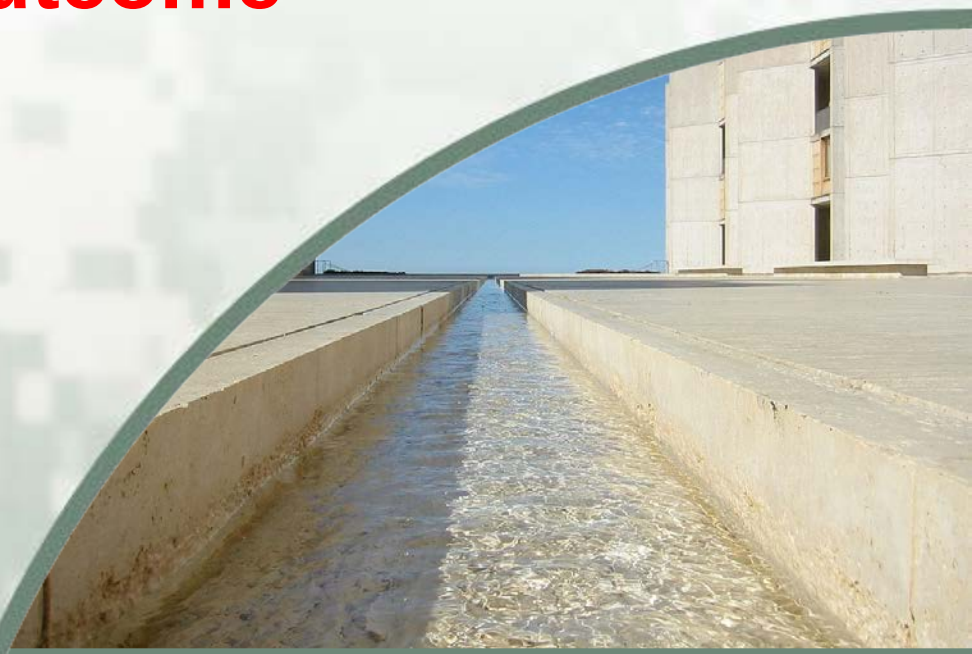

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Summary

- Majority of WoE frameworks have been qualitative in nature.
- We propose a quantitative WoE framework that utilizes MCDA methodology for integrating evidence underpinning KER within an AOP.
- We developed a prototype model that was parameterized by input from a few mode of action studies and judgments of individual experts.

Comparing WoE Approaches

Past

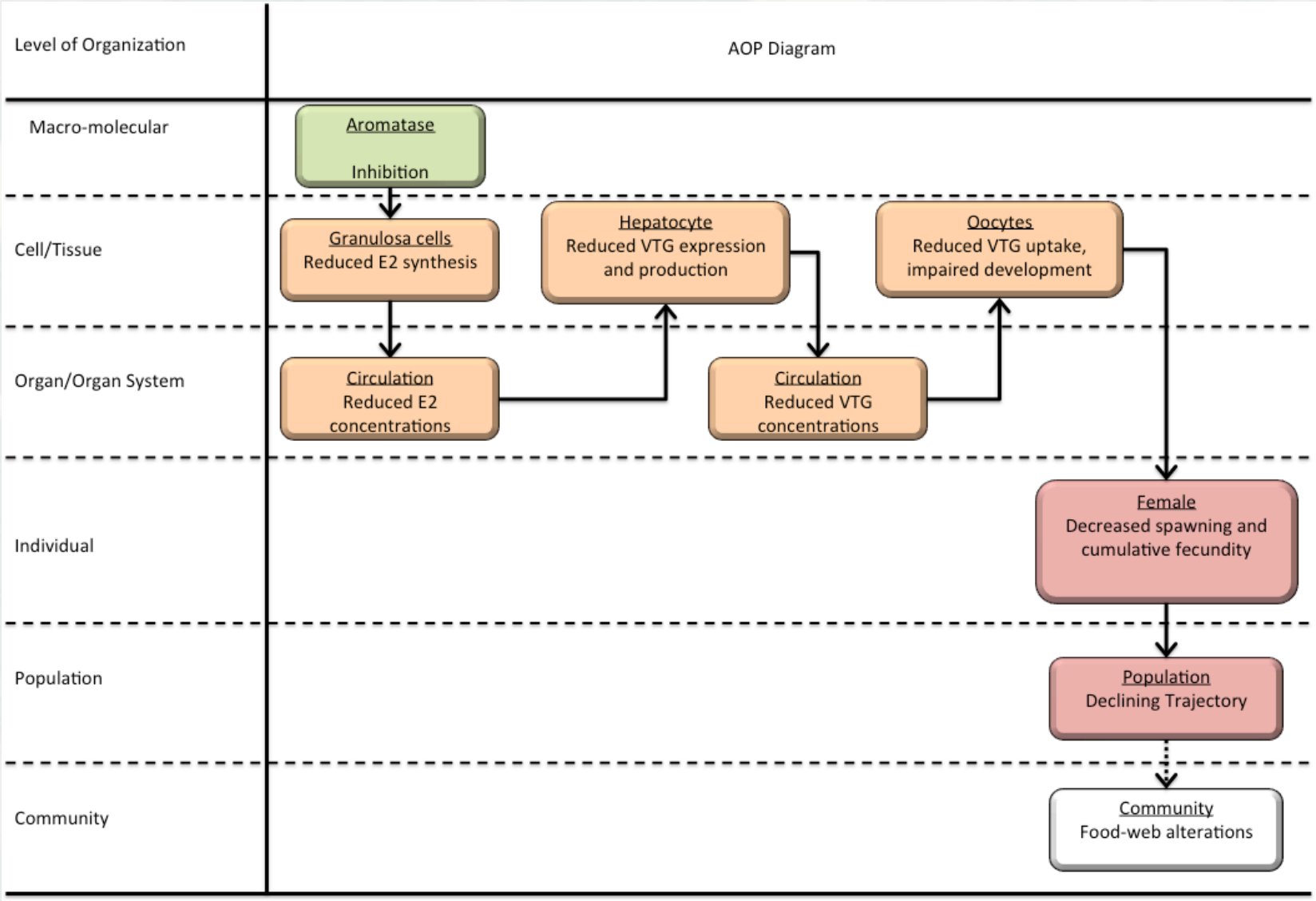
Present

Future

From Linkov et al., 2009

Linkov et al (in review)

Case Study: Aromatase inhibition leading to fish reproductive dysfunction



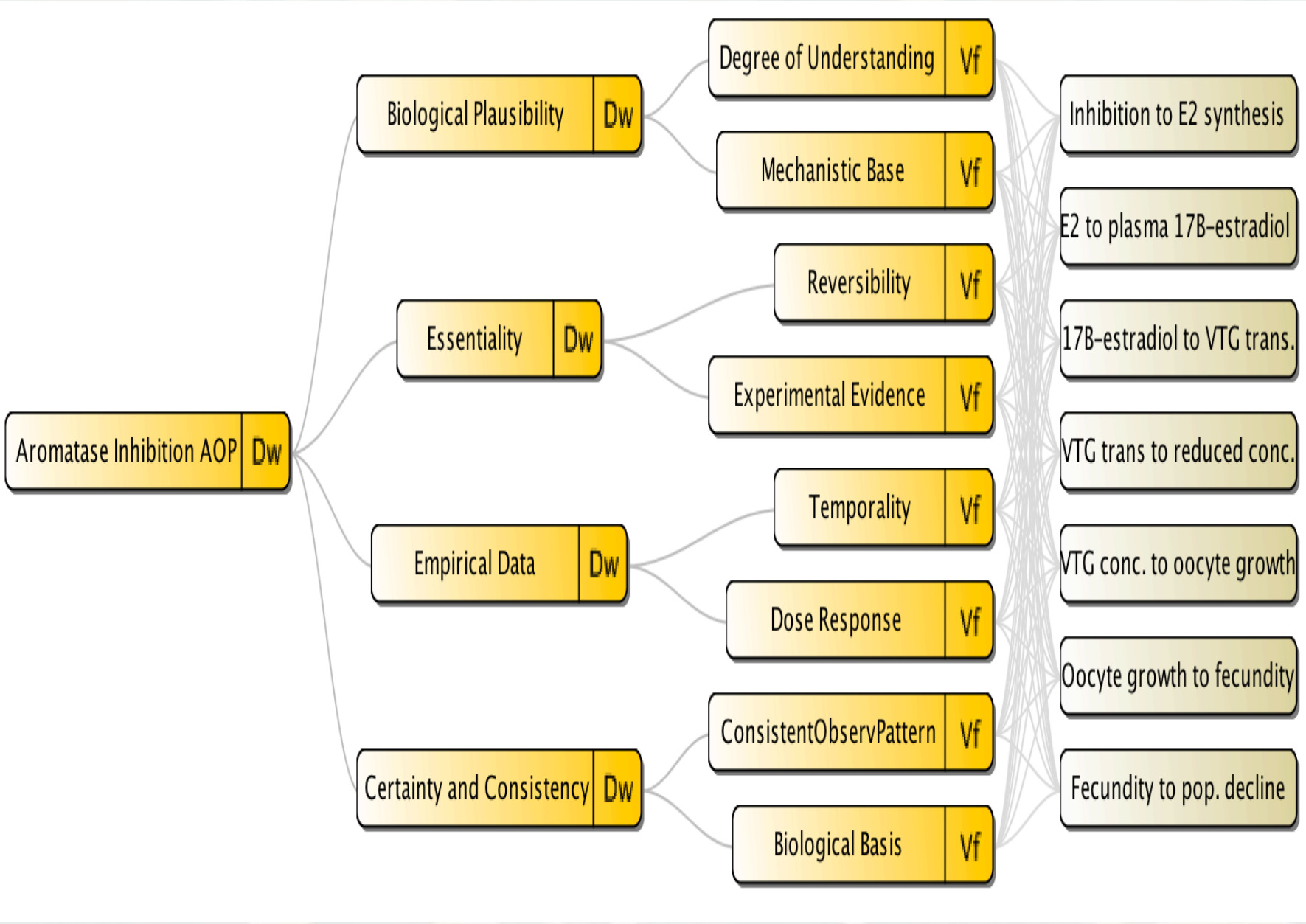
Logic Model Output

Key Event (upstream)	Key Event (downstream)	Weight-of-evidence for link
Aromatase inhibition	Ovarian (granulosa cell) E2 synthesis (reduction)	Strong
Ovarian (granulosa cell) E2 synthesis (reduction)	Plasma 17β-estradiol concentrations (reduction)	Strong
Plasma 17β-estradiol concentrations (reduction)	Transcription and translation of vitellogenin (reduction)	Strong
Transcription and translation of vitellogenin (reduction)	Plasma vitellogenin concentrations (reduction)	Strong
Plasma vitellogenin concentrations (reduction)	Vitellogenin uptake, impaired oocyte development (reduction)	Moderate
Vitellogenin uptake, impaired oocyte development (reduction)	Spawning and cumulative fecundity (reduction)	Moderate
Spawning and cumulative fecundity (reduction)	Population trajectory (declining)	Moderate

Steps of MCDA Methodology

1. Define KERs as alternatives for which relative confidence is unknown and needs to be prioritized
2. Map out the criteria and metrics based on BH considerations and KERs as a value tree
3. Assign weights for importance of each of the criteria and metrics associated with each criterion.
4. Score each KER based on each metric (In this case, Strong=3, Moderate=2, Weak=1)
5. Integrate scores and weights for each KER to assess overall confidence level
6. Conduct sensitivity analysis

MCDA Model


Aromatase Inhibition AOP
Dw
Biological Plausibility
Dw
Essentiality
Dw
Empirical Data
Dw
Certainty and Consistency
Dw
Degree of Understanding
Vf
Mechanistic Base
Vf
Reversibility
Vf
Experimental Evidence
Vf
Temporality
Vf
Dose Response
Vf
ConsistentObservPattern
Vf
Biological Basis
Vf
Inhibition to E2 synthesis
E2 to plasma 17B-estradiol
17B-estradiol to VTG trans.
VTG trans to reduced conc.
VTG conc. to oocyte growth
Oocyte growth to fecundity
Fecundity to pop. decline

Criteria Weights and Key Event Scores

Direct weighting - Empirical Data

Set weights directly

Criterion	Weight	
Temporality	0.500	0.500
Dose Response	0.500	0.500

Direct weighting - Aromatase Inhibition AOP

Set weights directly

Criterion	Weight	
Biological Plausibility	0.400	0.400
Essentiality	0.300	0.300
Empirical Data	0.200	0.200
Certainty and Consistency	0.100	0.100

Scores/Performances - Degree of Understanding

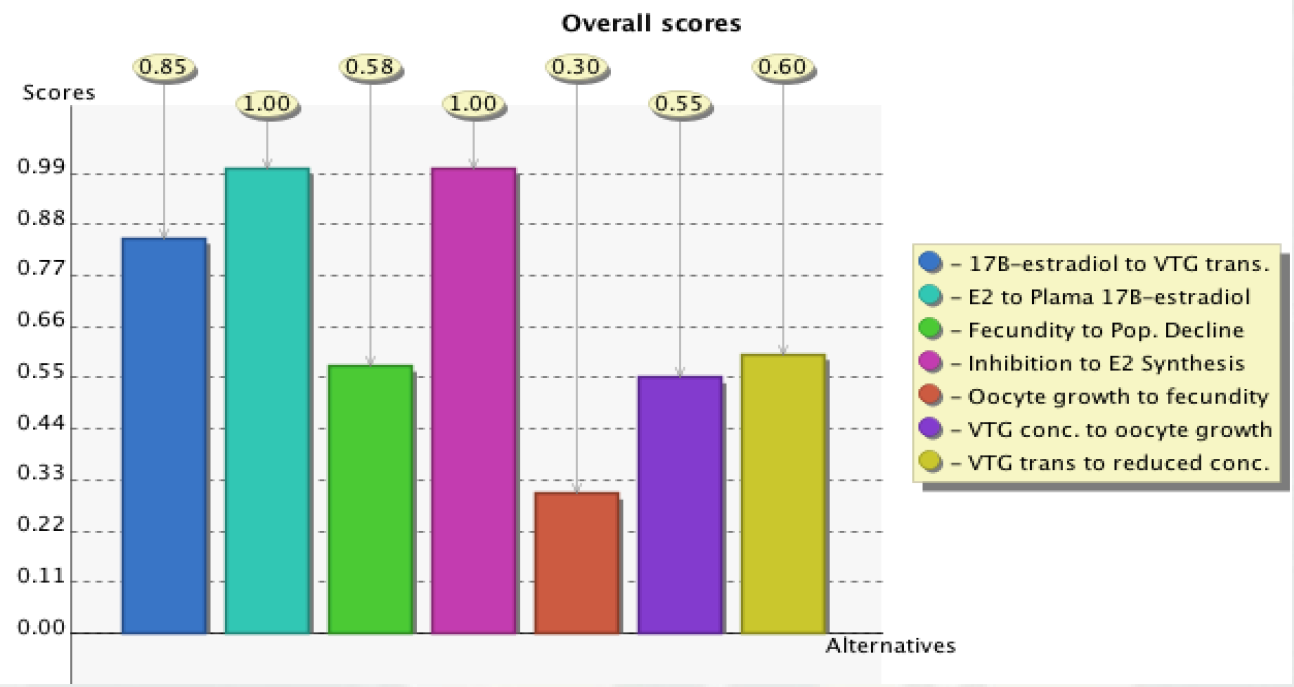
Scores | Value function

Set scores directly

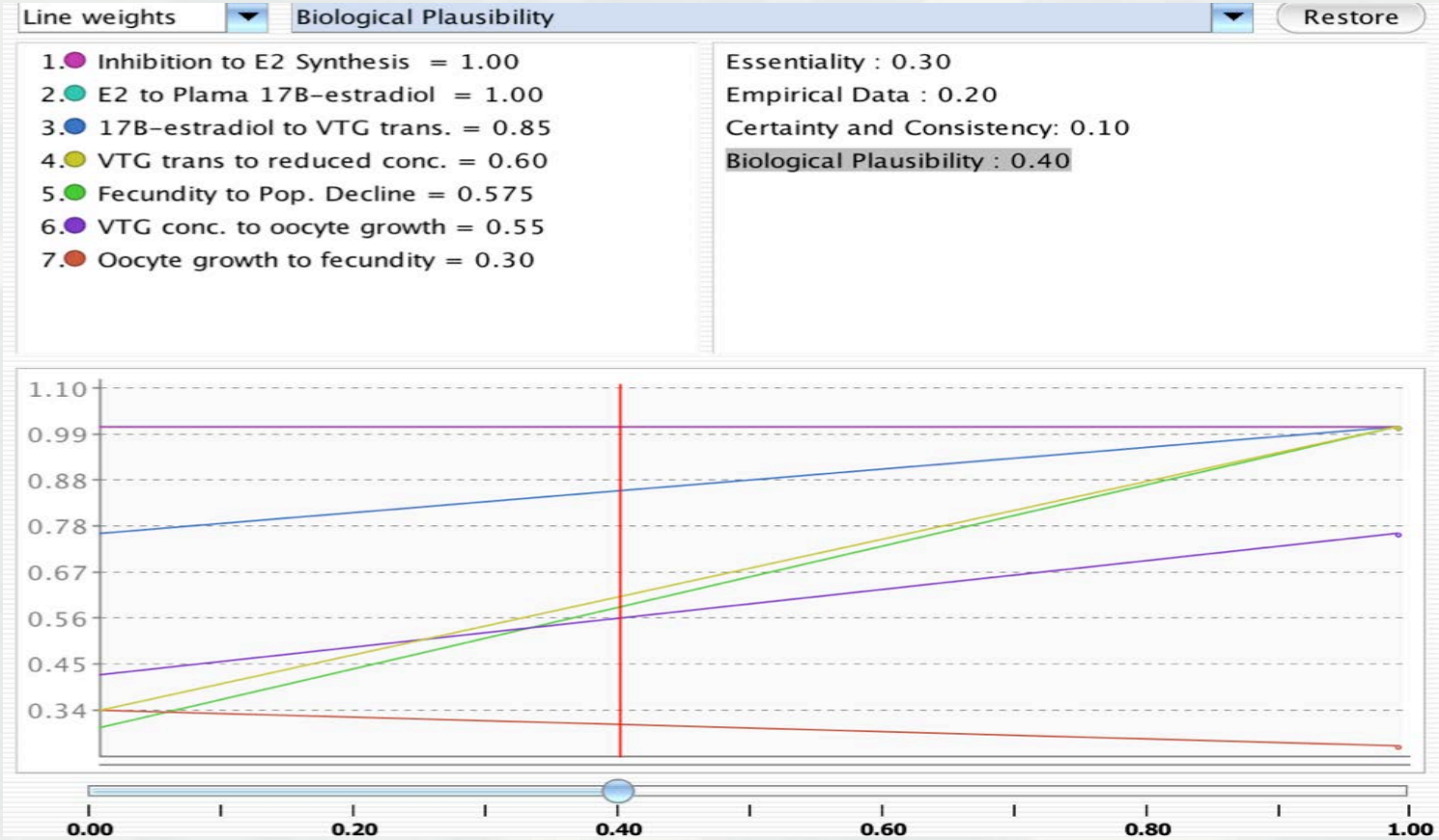
Alternatives performances and scores

Alternative	Current	Score
Inhibition to E2 Synthesis	3.000	1.000
E2 to Plama 17B-estradiol	3.000	1.000
17B-estradiol to VTG trans.	3.000	1.000
VTG trans to reduced conc.	3.000	1.000
VTG conc. to oocyte growth	3.000	1.000
Oocyte growth to fecundity	2.000	0.000
Fecundity to Pop. Decline	3.000	1.000

Confidence Assessment Scores



Sensitivity Analysis



Conclusions

- Quantitative WoE frameworks provide an objective and transparent mean to assess AOPs
- MCDA strengthens WoE logic by adding visual effect of a mapped decision structure as well as quantitative weighing of LOE
- Restricts expert inputs to weighing evidence
- Allows for incorporation of inputs from multiple experts

References

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