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Motivation

- QSP models often contain large numbers of states and parameters
- Resulting practical problems:
 - High computational cost
 - Unidentifiable parameters
 - Difficult to interpret dynamics

→ Apply model order reduction

Objectives

- Use state-level reduction approaches to retain mechanistic meaning of states
- Combine them in one procedure to leverage their distinct strengths and achieve better reductions
- Develop automated procedure
- Evaluate procedure on large-scale QSP model [1]

Notation

QSP model:

- X : All states
- X_i : State i
- k : Parameters
- $t \in [0, T]$: Timespan
- $X_0 = X(0)$: Init. condition
- ε : Error
- δ : Error bound

Abbreviations:

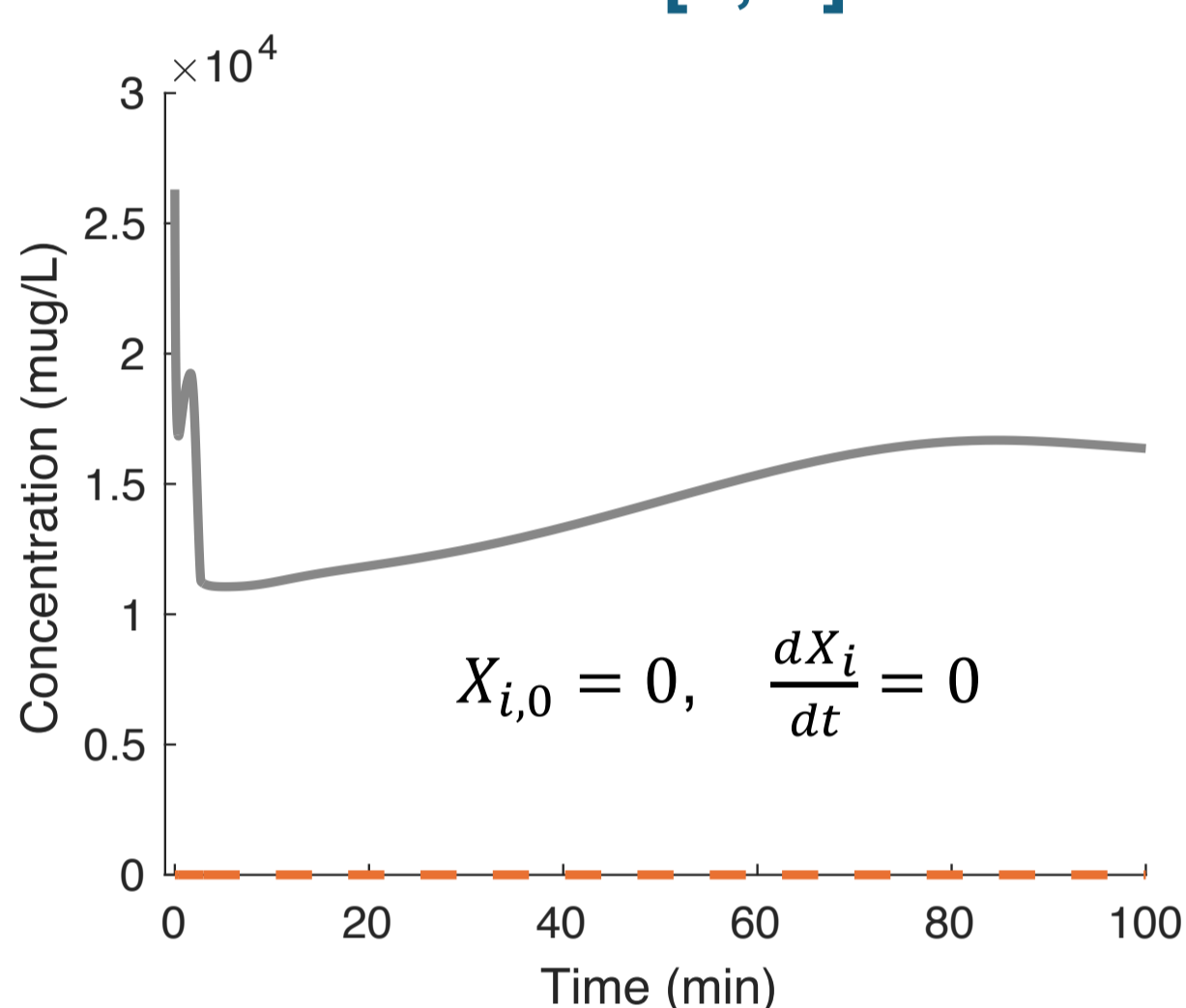
- f_{obj} : Objective function
- OFV: Objective function value
- out : Output
- rem : Remaining
- red : Reduced

State-level reduction approaches:

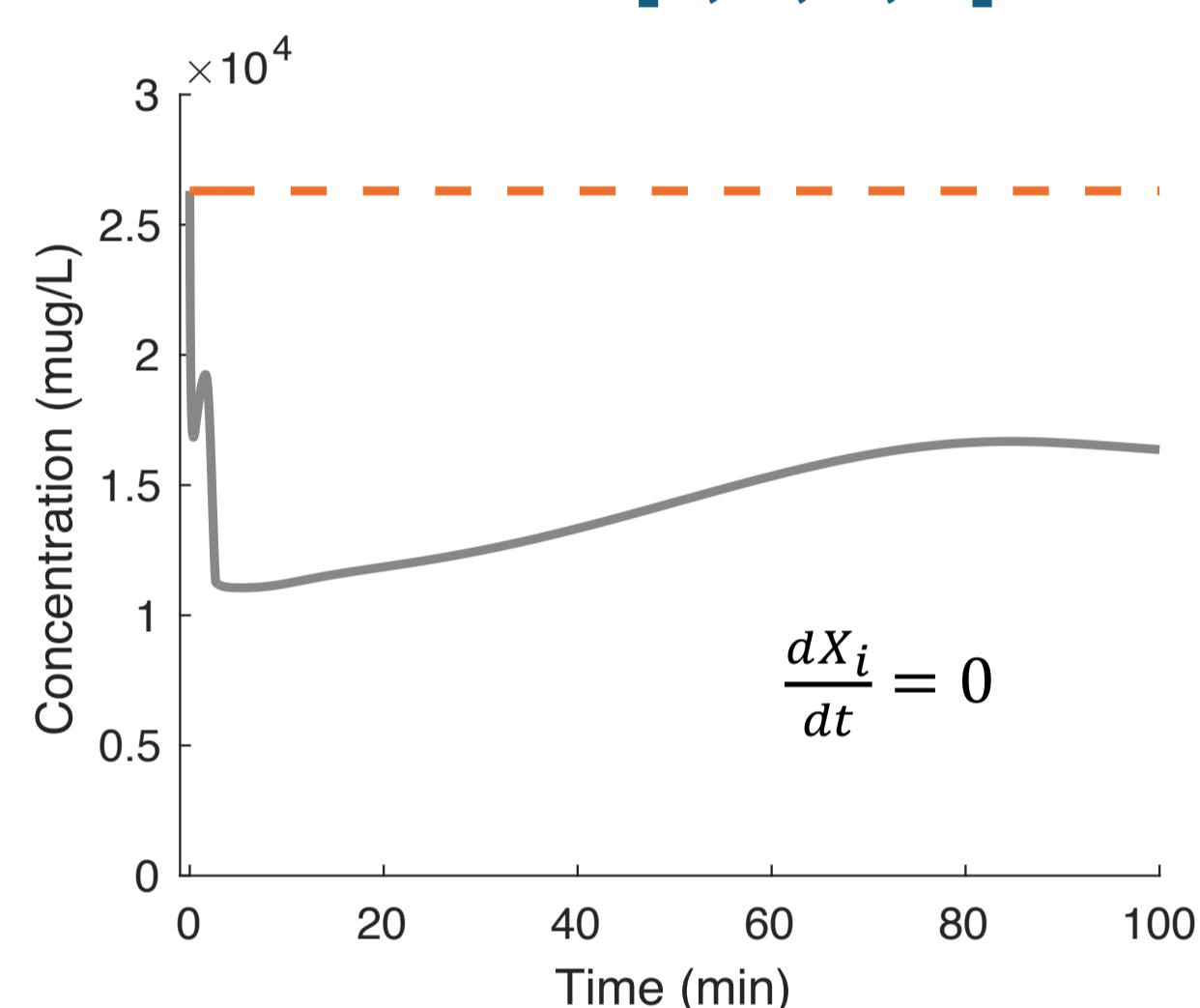
- NEG: Neglected state
- ENV: Environmental state
- QSS: Quasi-steady state
- OENV: Observability-weighted environmental state

State-level reduction approaches

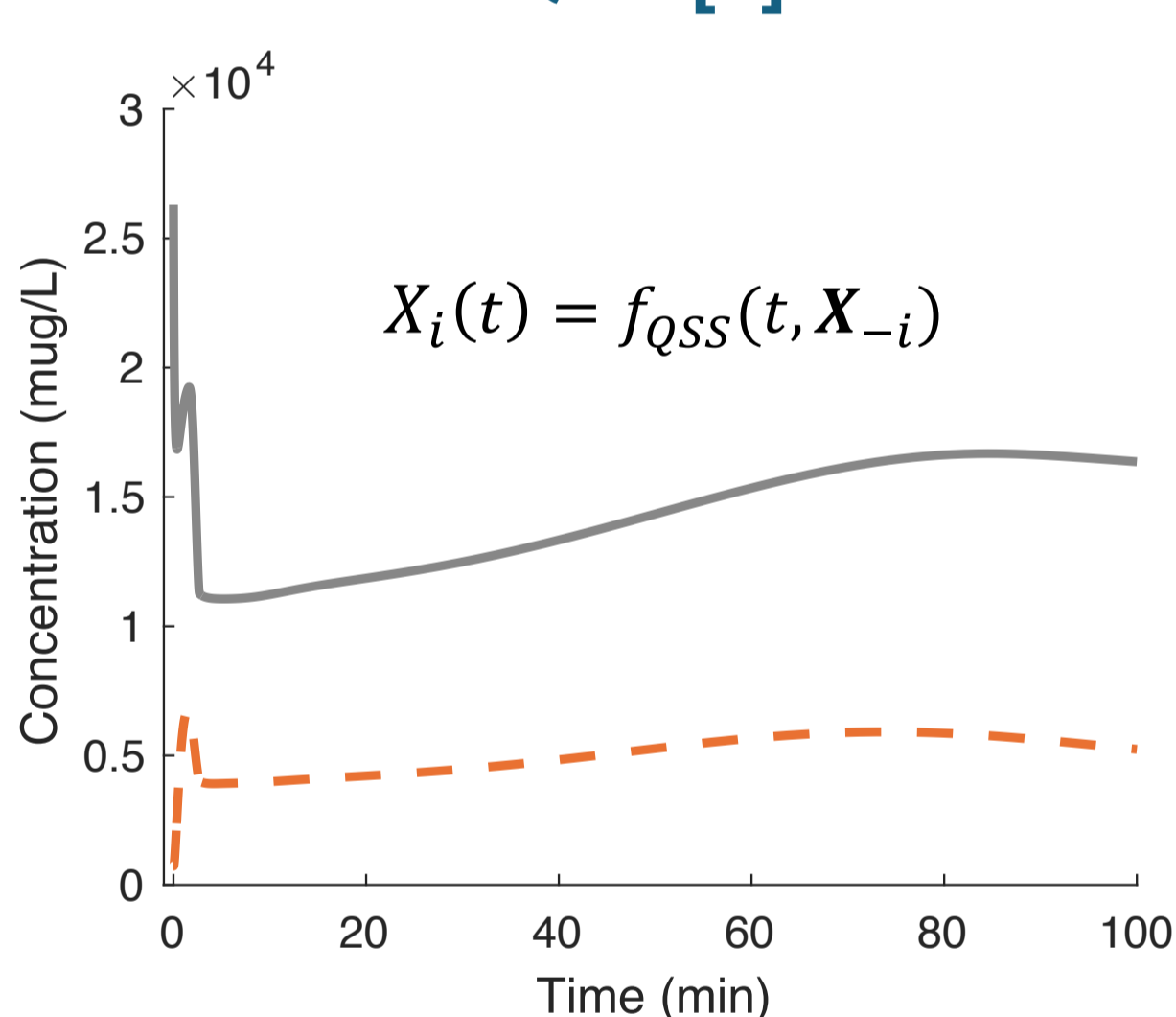
NEG [2, 3]



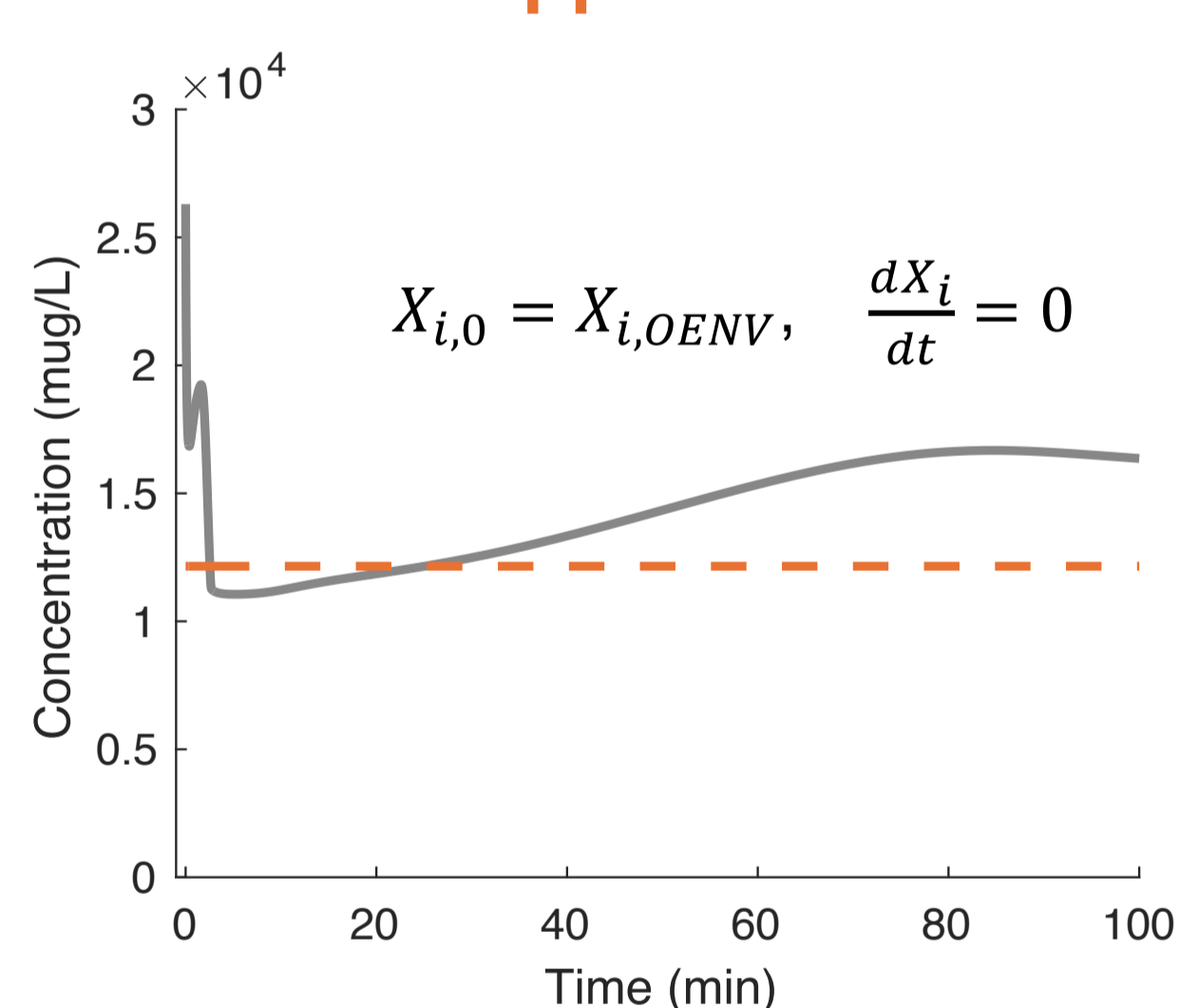
ENV [2, 3, 4, 5]



QSS [6]



Novel approach: OENV



Combined reduction procedure

1: Set hyperparameters

- Relevant output states
- Output states error bound δ_{out}
- Remaining states error bound δ_{rem}
- Error function

$$\varepsilon_i(X_i, X_{i,red}) = \int_0^T \frac{(X_i - X_{i,red})^2}{X_i} dt$$

- Objective function

$$f_{obj}(\varepsilon_{out}, \varepsilon_{rem}) = \frac{\varepsilon_{out}}{\delta_{out}} + \alpha \frac{\varepsilon_{rem}}{\delta_{rem}}$$

3: Examine reduced model

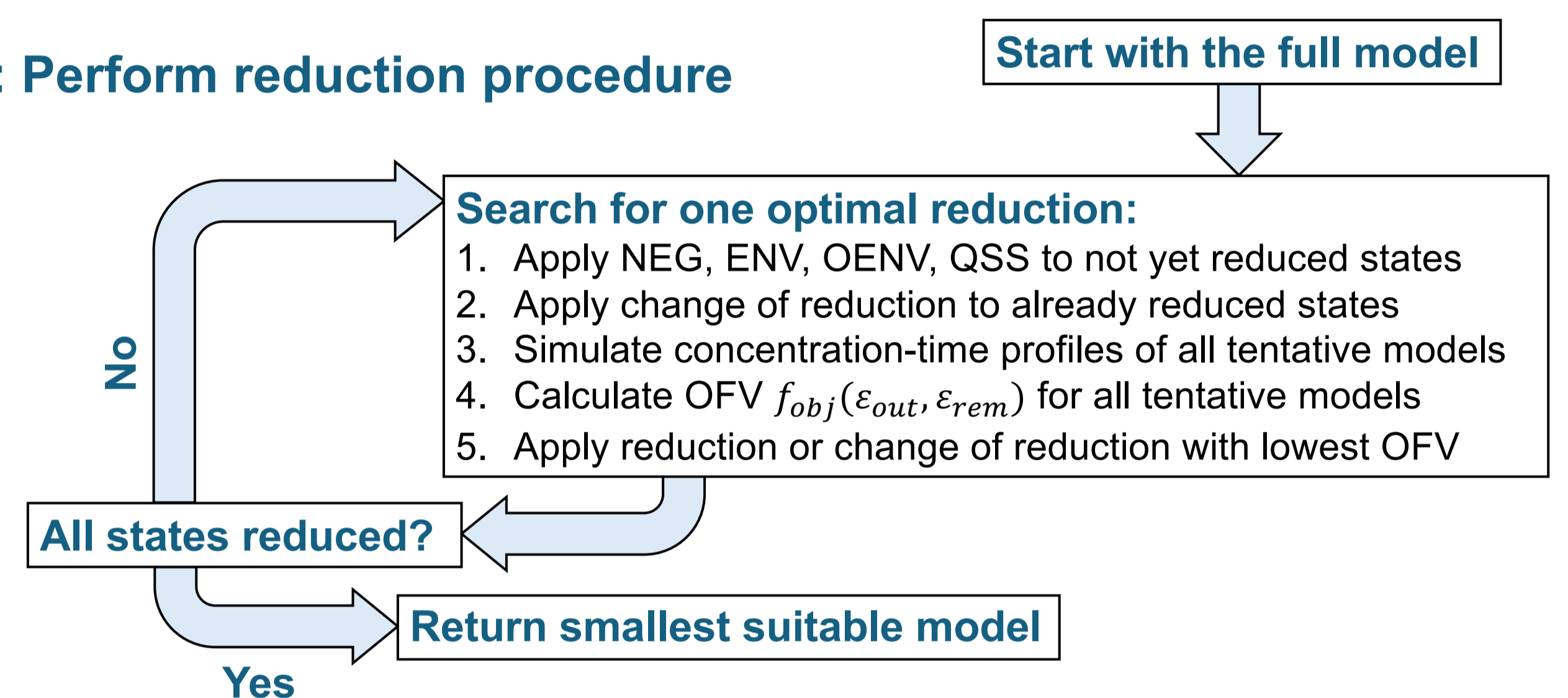
If relevant endpoints poorly approximated:

- Decrease δ_{out} and/or δ_{rem}
- Change error function
- Change objective function

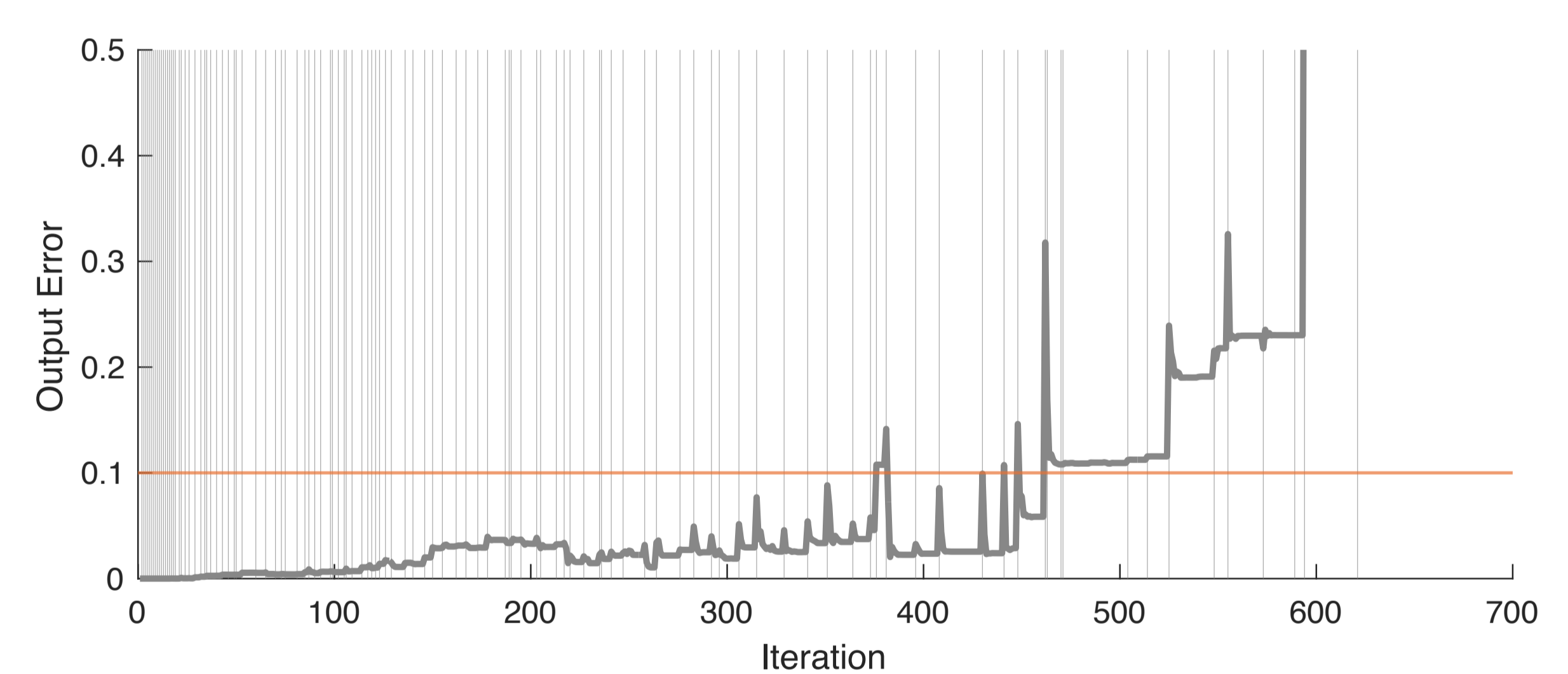
If long computation time:

- Reduce without QSS

2: Perform reduction procedure

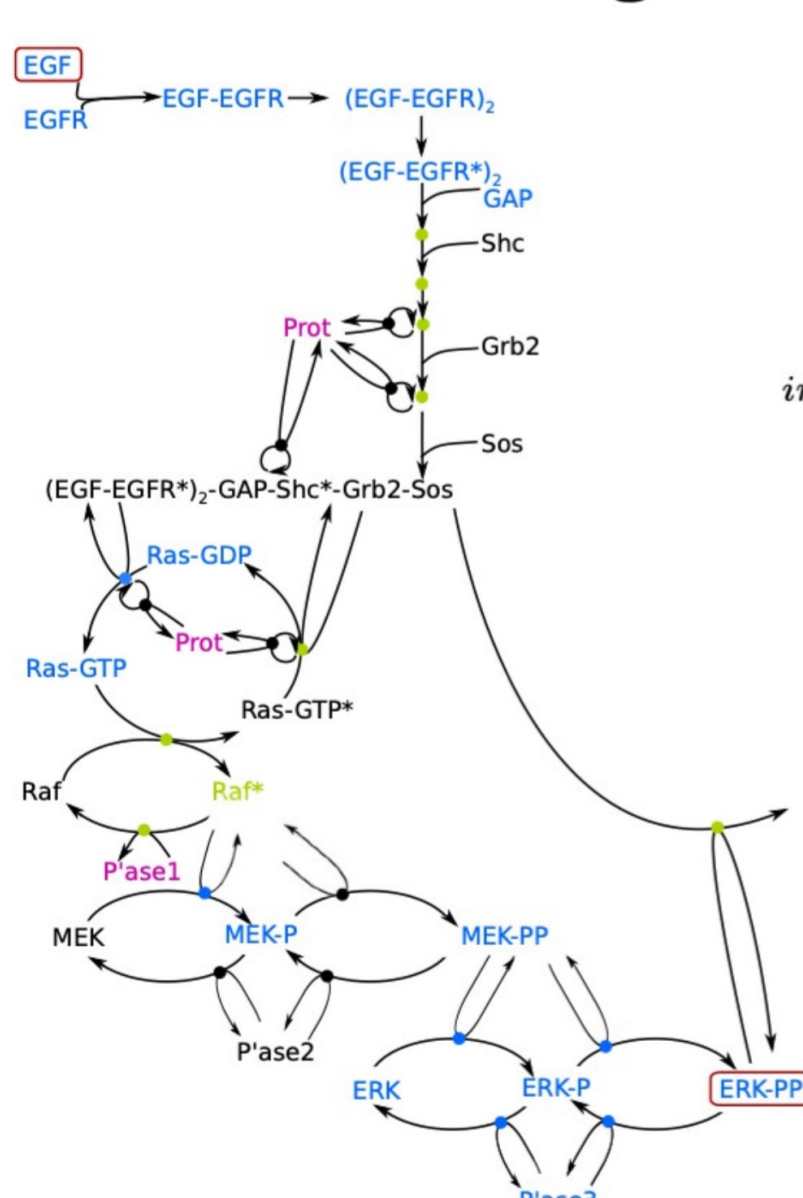


Error can fall while reducing → Iterate until the end

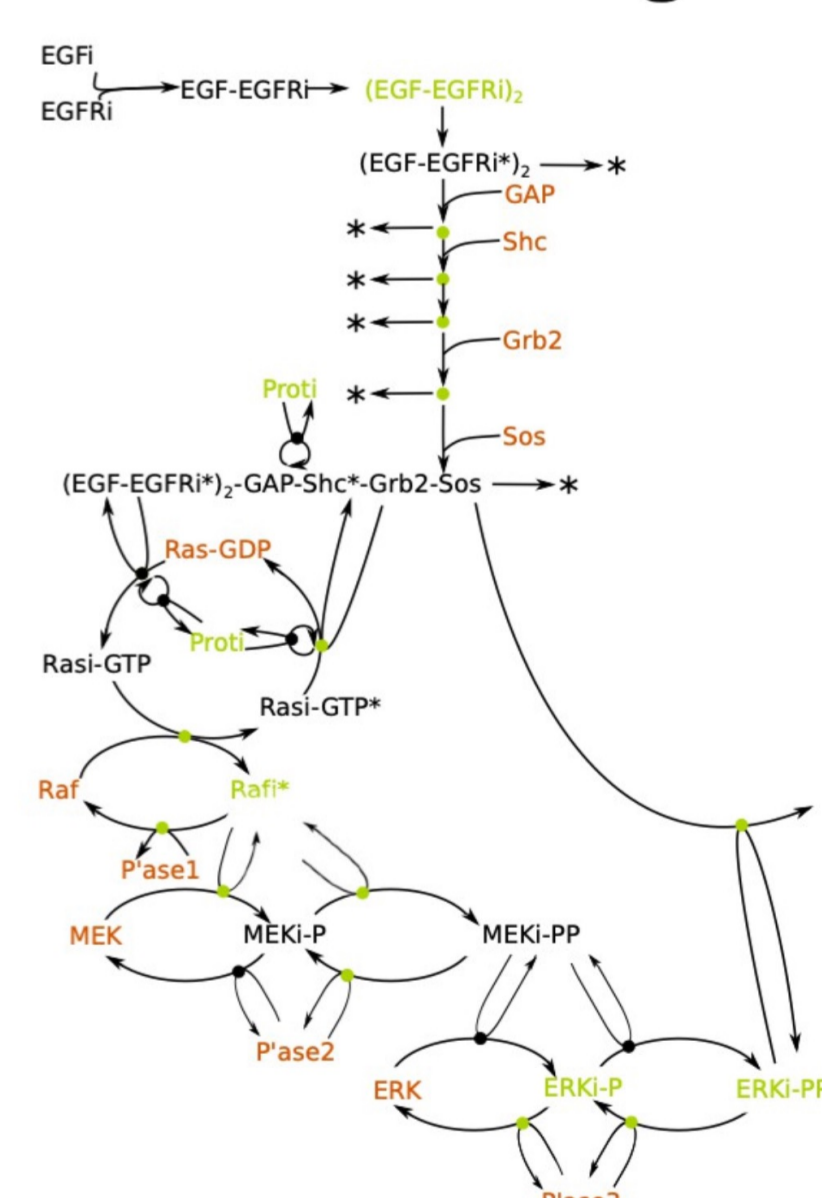


Reducing a model of EGFR signalling

(A) membrane EGFR signalling



(B) internalised EGFR signalling



No. of states: 111
No. of parameters: 247

Input: 5 mg/L EGF (epidermal growth factor)
Output: ERK_PP (activated extracellular signal-regulated kinase)

Dynamic properties:

- Two signalling cascades
- Long reaction chains
- Feedback loops
- Nonlinear dynamics

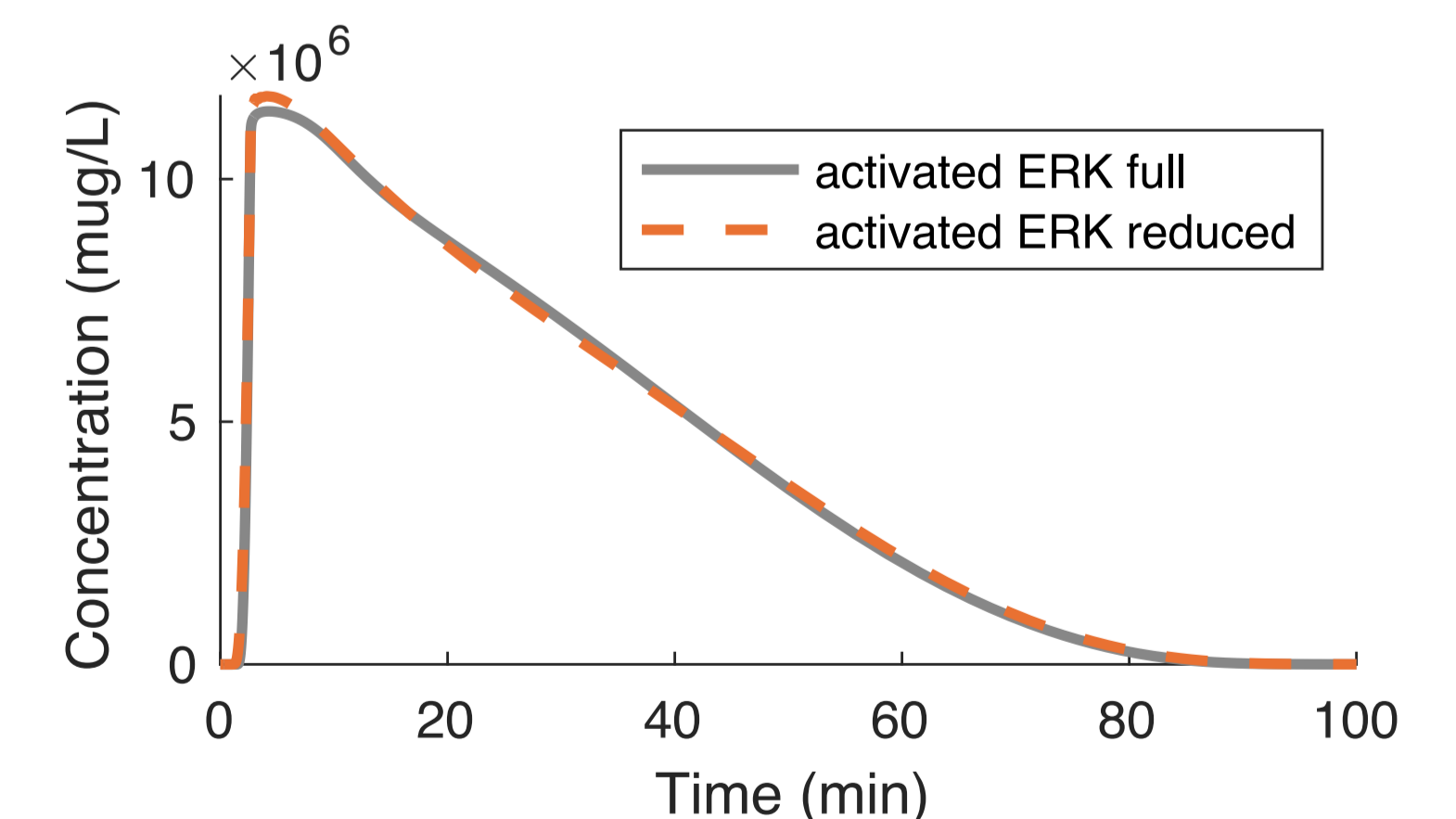
Depicted are the most influential cell membrane (A) and internalised (B) species according to index analysis [7].

Reduction results

	NEG + ENV	+ QSS	+ OENV
No. of states:	55	34	15
No. of parameters:	115 + 5	188 + 4	111 + 4 + 15
(parameters + ENV + OENV states)			
Output error ε_{out} :	2.4 %	2.2 %	2.4 %
Mean remaining error:	16.3 %	20.3 %	17.6 %
Max remaining error ε_{rem} :	49.9 %	49.9 %	44.8 %

Hyperparameters:

$\alpha = 1$
 $\delta_{out} = 10\%$
 $\delta_{rem} = 50\%$



Conclusion

- Automated procedure was developed which effectively integrates multiple state-level reduction approaches
- EGFR model: output is well-approximated and average error of remaining states is limited while achieving a strong reduction

→ Combining multiple state-level reduction approaches yields stronger reductions

Next steps

- Integrate conservation laws as additional state-level reduction approach
- Reduction with respect to a virtual population, similar to [3] (for now only with respect to reference parameters)
- Monitor error of multiple endpoints
- Reduction such that perturbation of different drugs to different potential targets well approximated

References:

- [1] Hornberg et al., Oncogene, 2005
[2] Knöchel et al., Journal of Pharmacokinetics and Pharmacodynamics, 2018
[3] Falkenhagen et al., CPT: Pharmacometrics & Systems Pharmacology, 2023
[4] Danø et al., The FEBS Journal, 2006

- [5] Taylor et al., Biophysical Journal, 2008
[6] Snowden et al., Bulletin of Mathematical Biology, 2017
[7] Knöchel et al., PLOS Computational Biology, 2024