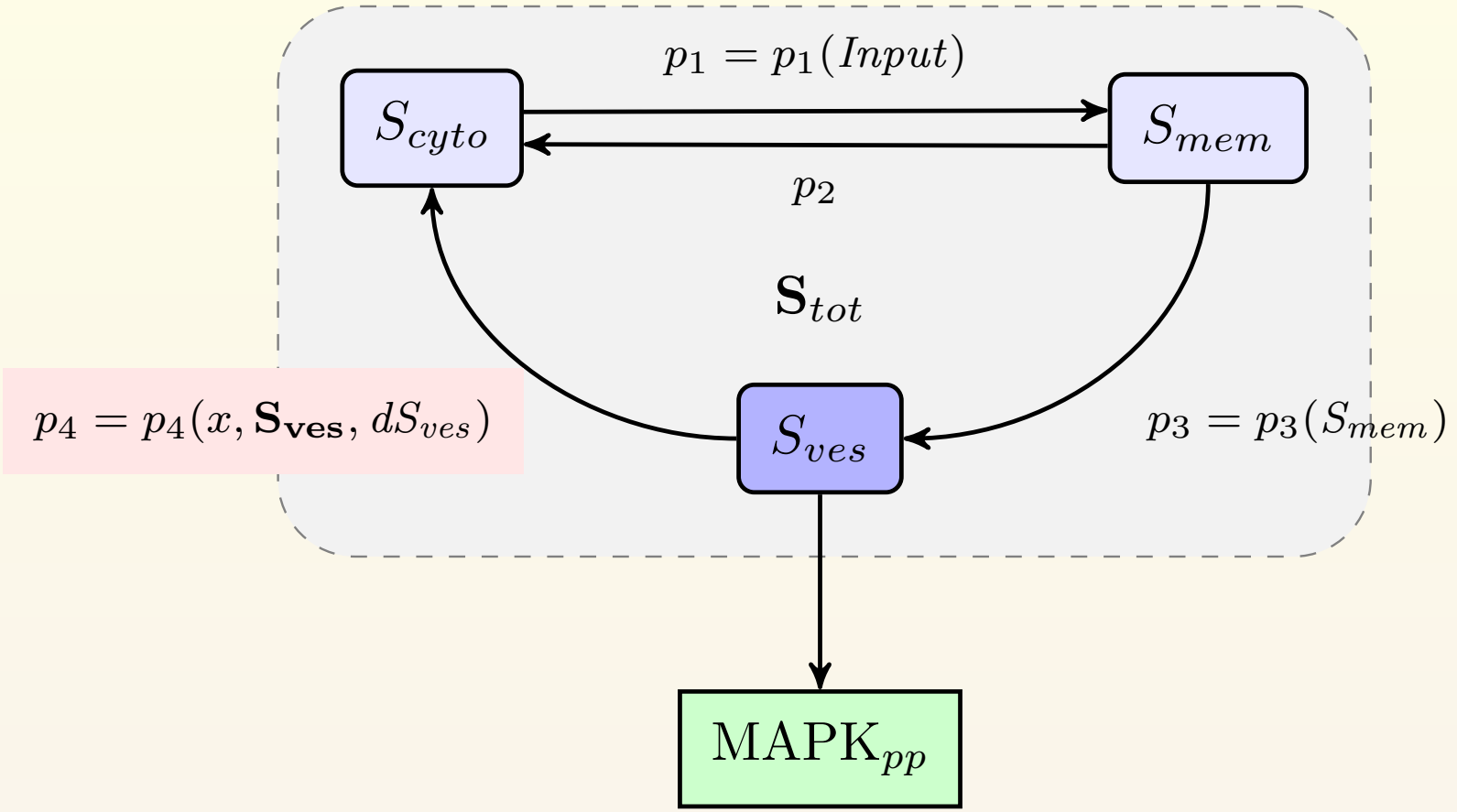
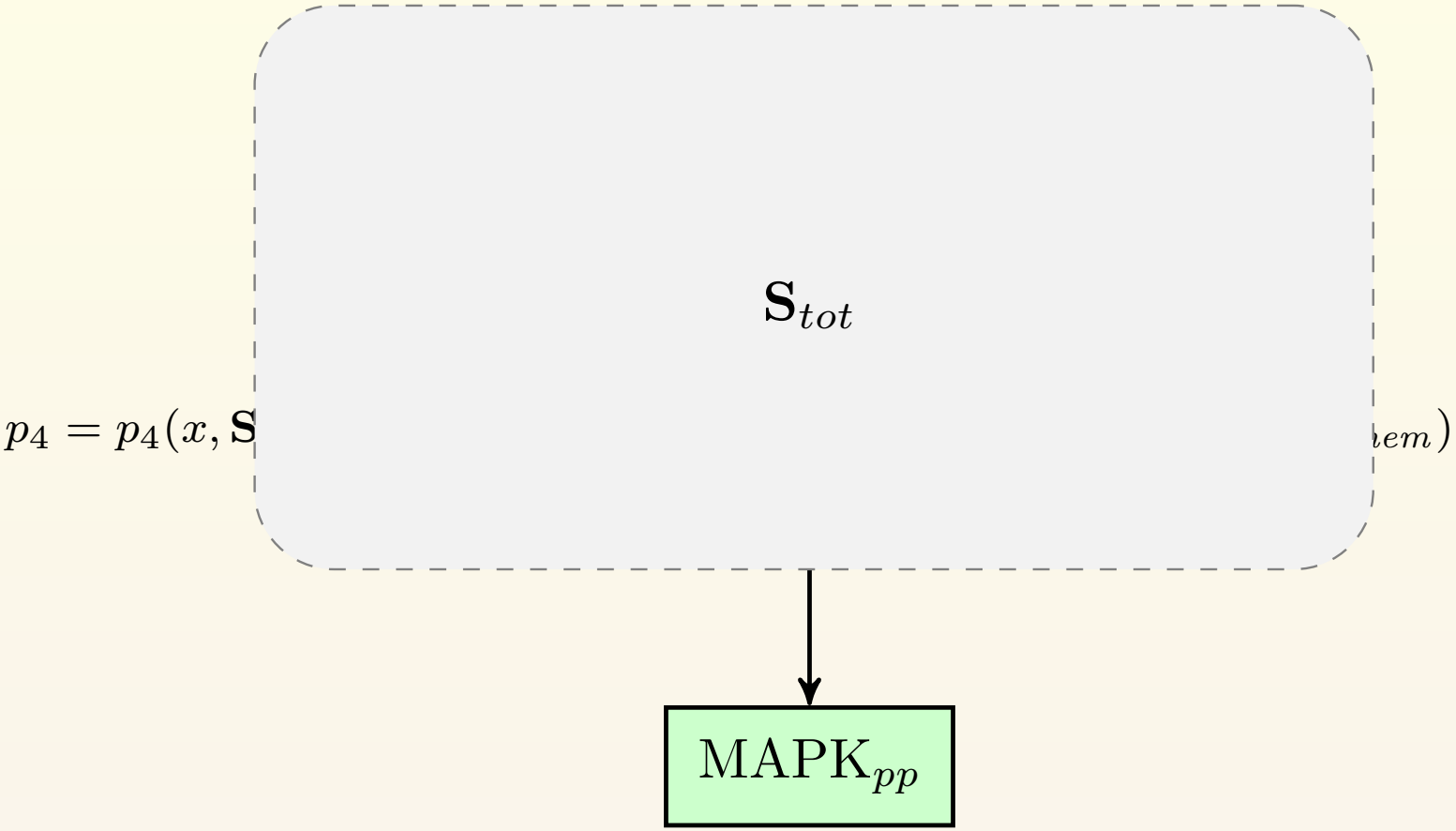
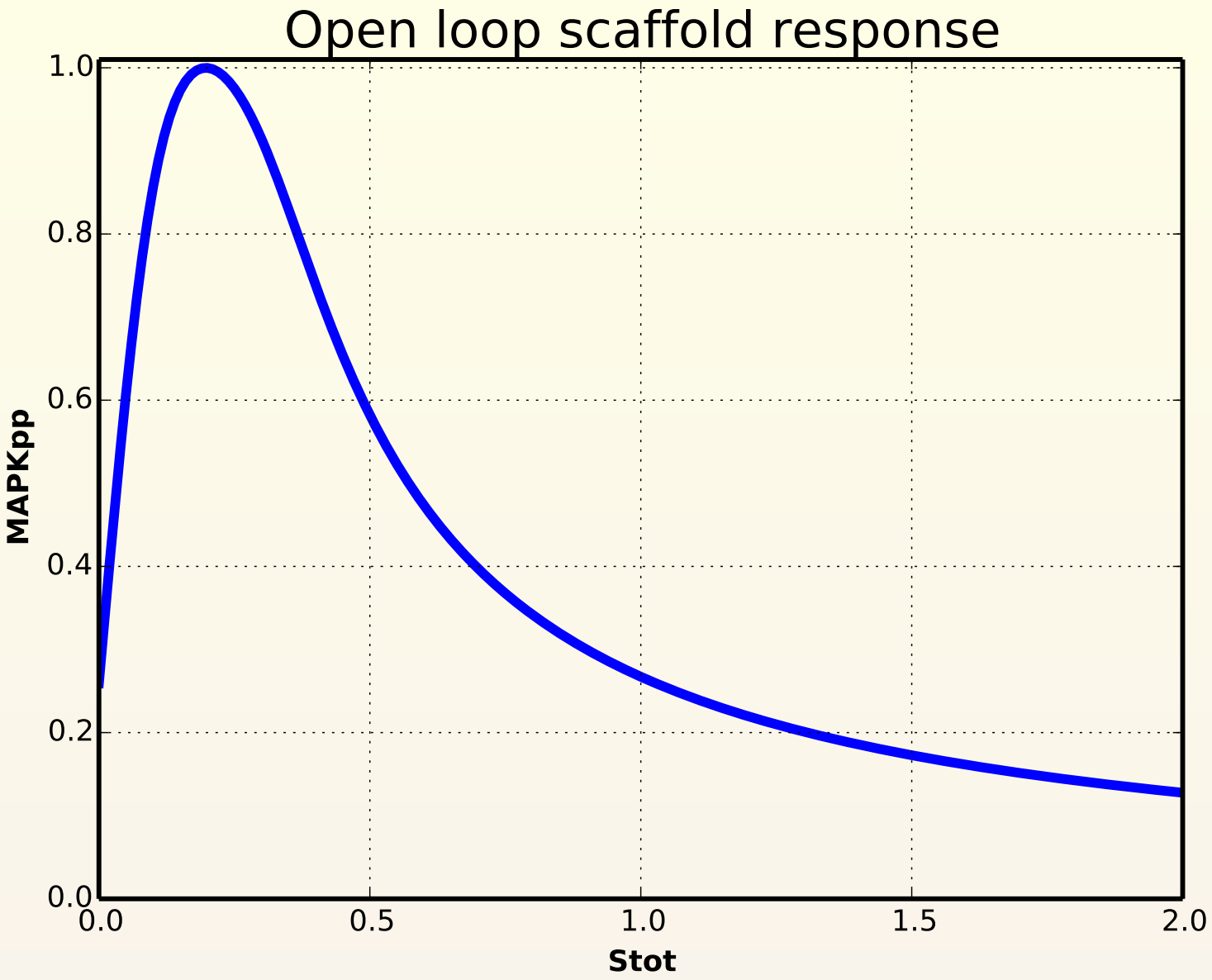
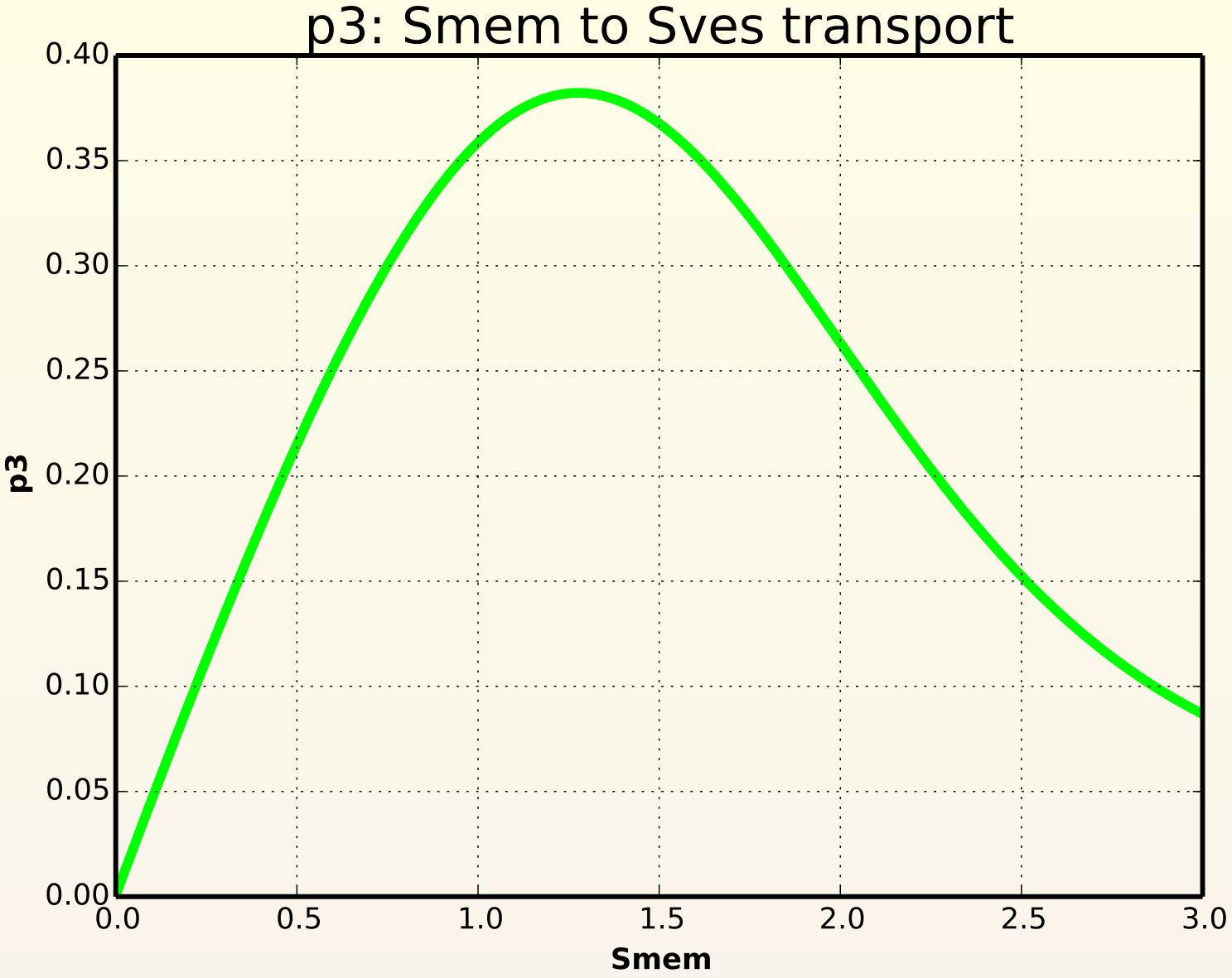
Model Schematic



Open Loop Response

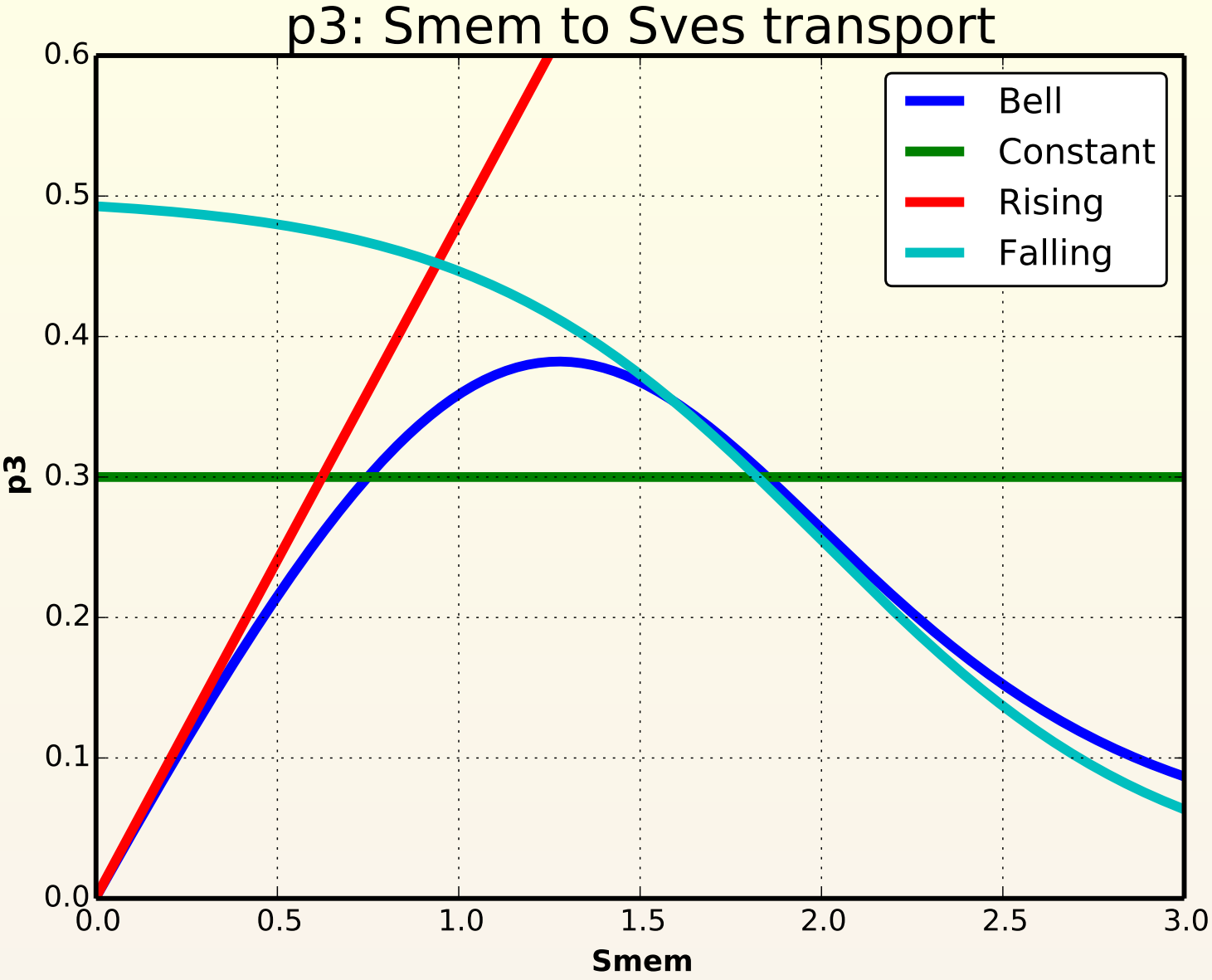


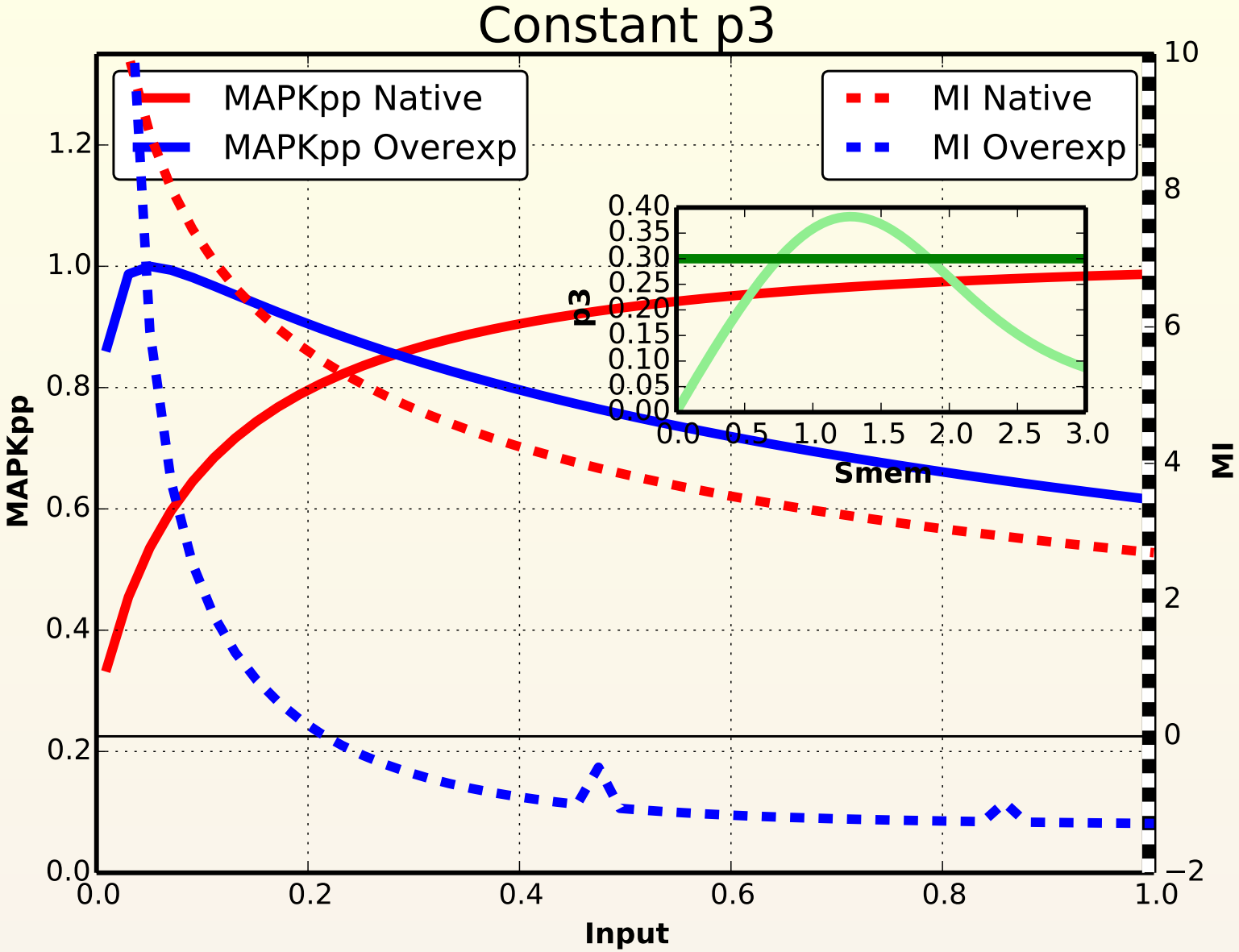

Open loop scaffold response
MAPKpp
Stot
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0


p3: Smem to Sves transport
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
p3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Smem

Why is p3 a bell shaped response?

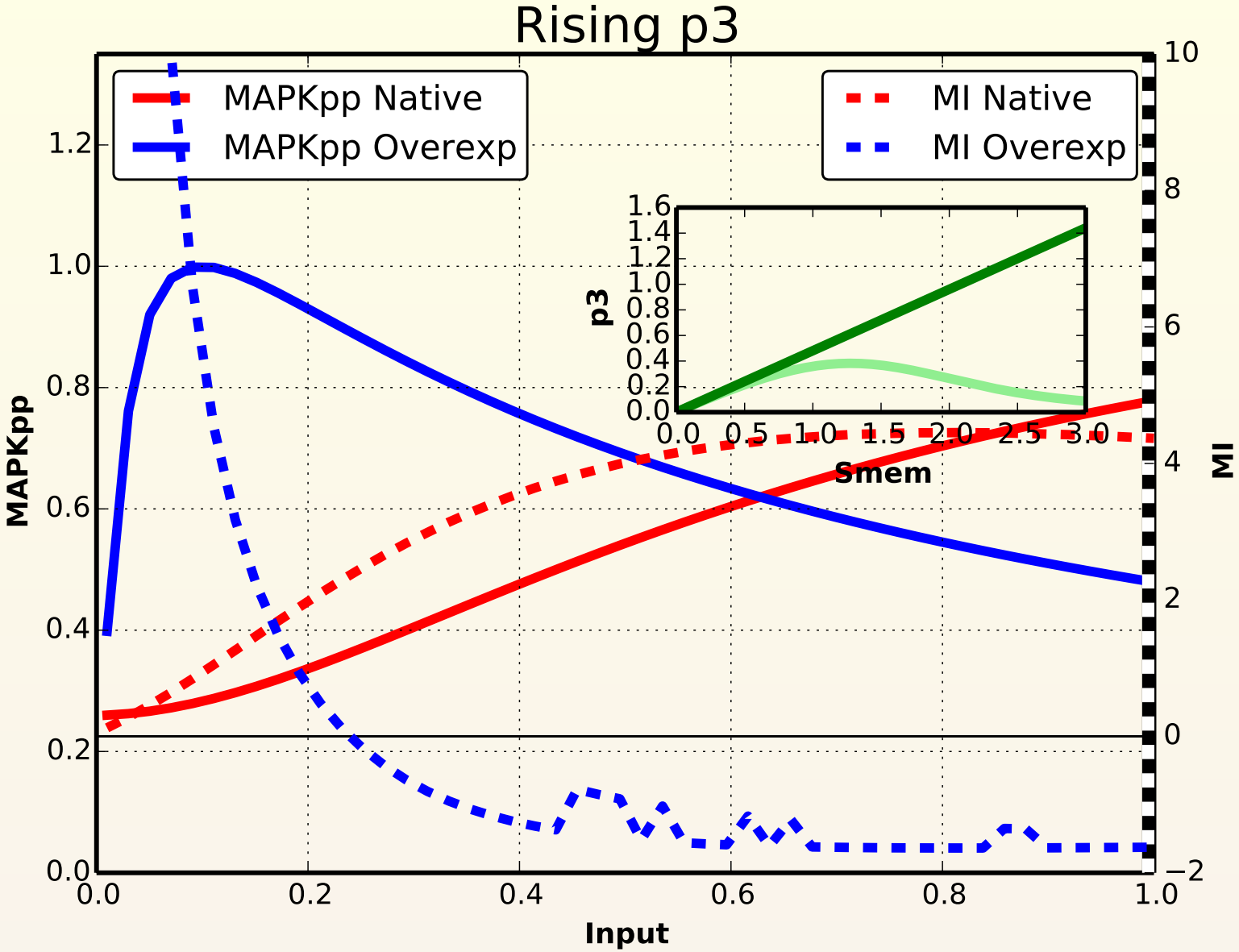
- Each part of the bell shaped curved is simulated to justify its use
  - Constant term
  - Linear rising term
  - Just the falling side
  - Bell shape
    - ★ by combining the rising and falling terms


p3: Smem to Sves transport
Bell
Constant
Rising
Falling
p3
Smem
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.0
0.5
1.0
1.5
2.0
2.5
3.0


Constant p3
MAPKpp Native
MAPKpp Overexp
MI Native
MI Overexp
MAPKpp
MI
Input
p3
Smem
0.0
0.2
0.4
0.6
0.8
1.0
1.2
−2
0
2
4
6
8
10
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.5
1.5
2.0
2.5
3.0

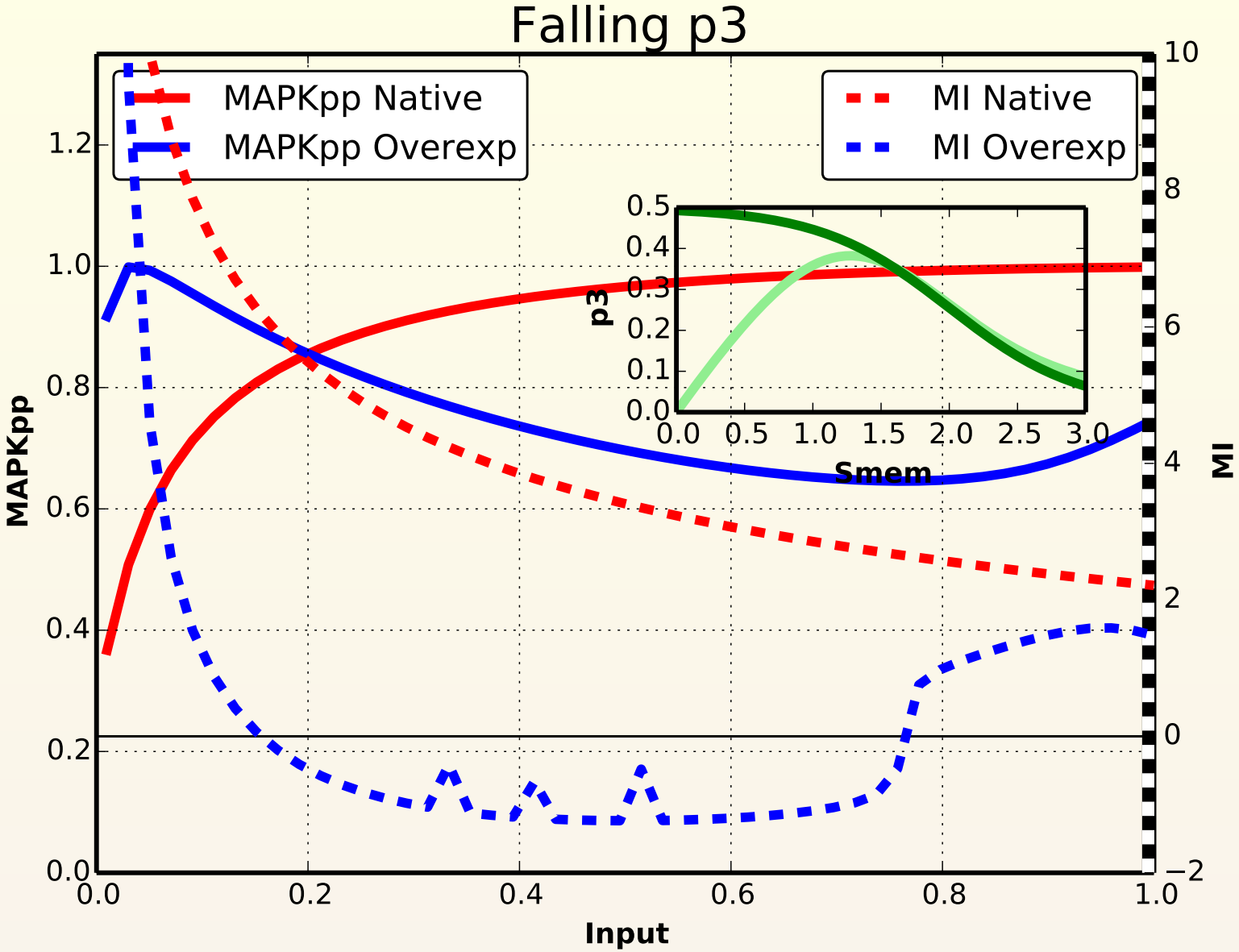
Results for constant p3

- At native levels, we get a saturating increase in MAPKpp, producing a negatively sloping MI curve
  - Experimentally MI is constant w.r.t. dose
- At overexpressed levels, the simulation only produces negative MI values
  - Experimentally MI goes from negative to positive


Rising p3
MAPKpp Native
MAPKpp Overexp
MI Native
MI Overexp
MAPKpp
MI
Input
p3
Smem
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
0.5
1.5
2.0
2.5
3.0
8
6
4
2
0
−2
10

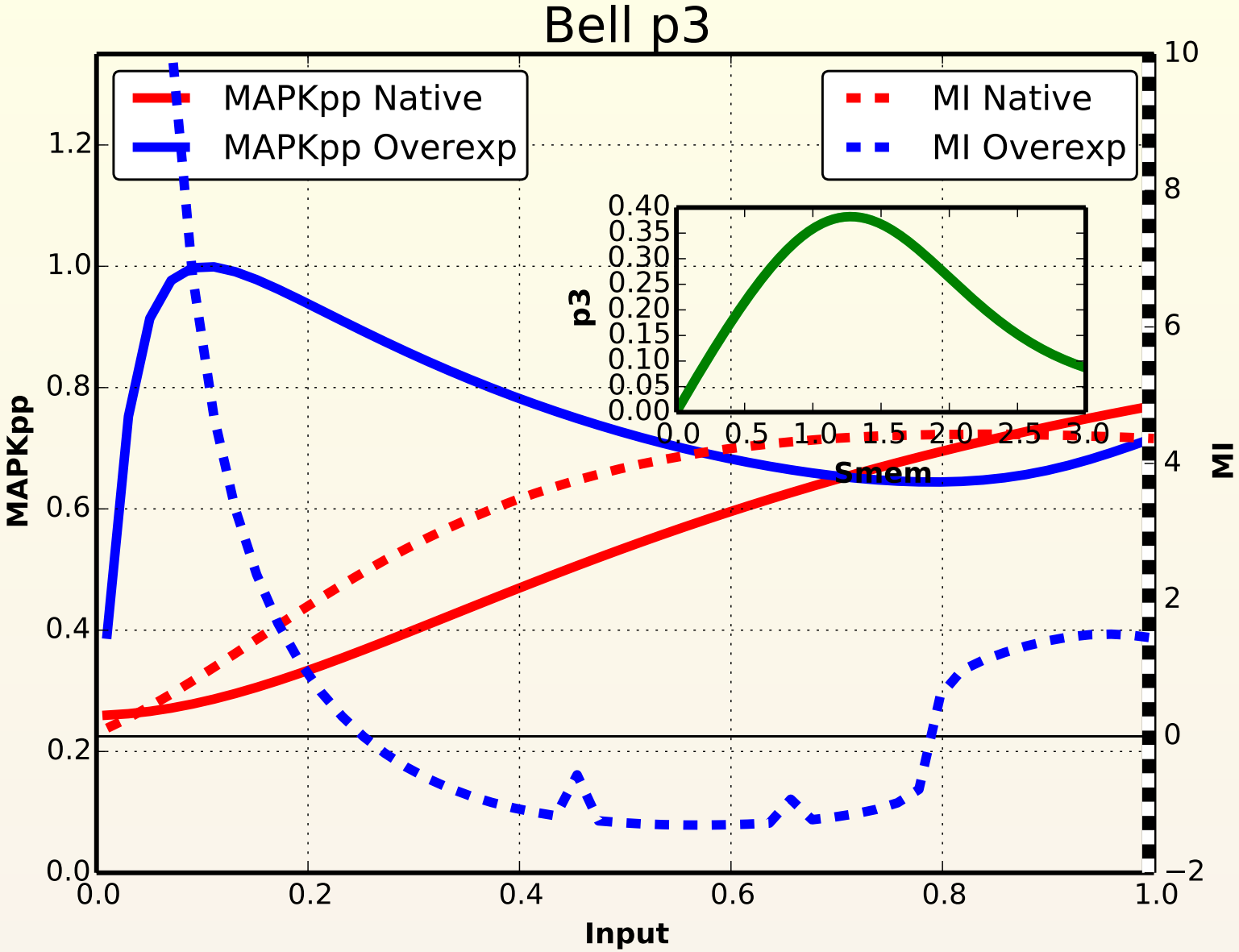
Results for rising p3

- At native levels, MAPKpp now rises linearly with dose, producing a flat MI response since it is the derivative
  - This is what is observed experimentally
- At overexpressed levels, the simulation still only produces negative MI values
  - Experimentally MI goes from negative to positive


Falling p3
MAPKpp Native
MAPKpp Overexp
MI Native
MI Overexp
MAPKpp
MI
Input
p3
Smem
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.5
0.1
0.3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
10
8
6
4
2
0
−2

Results for falling p3

- At native levels, MAPKpp saturates rapidly just like the constant case, producing a decreasing MI response
  - MI should be constant
- At overexpressed levels, MAPKpp is now able to rise at high inputs after falling, producing a MI response that goes from negative to positive
  - Experimentally MI goes from negative to positive

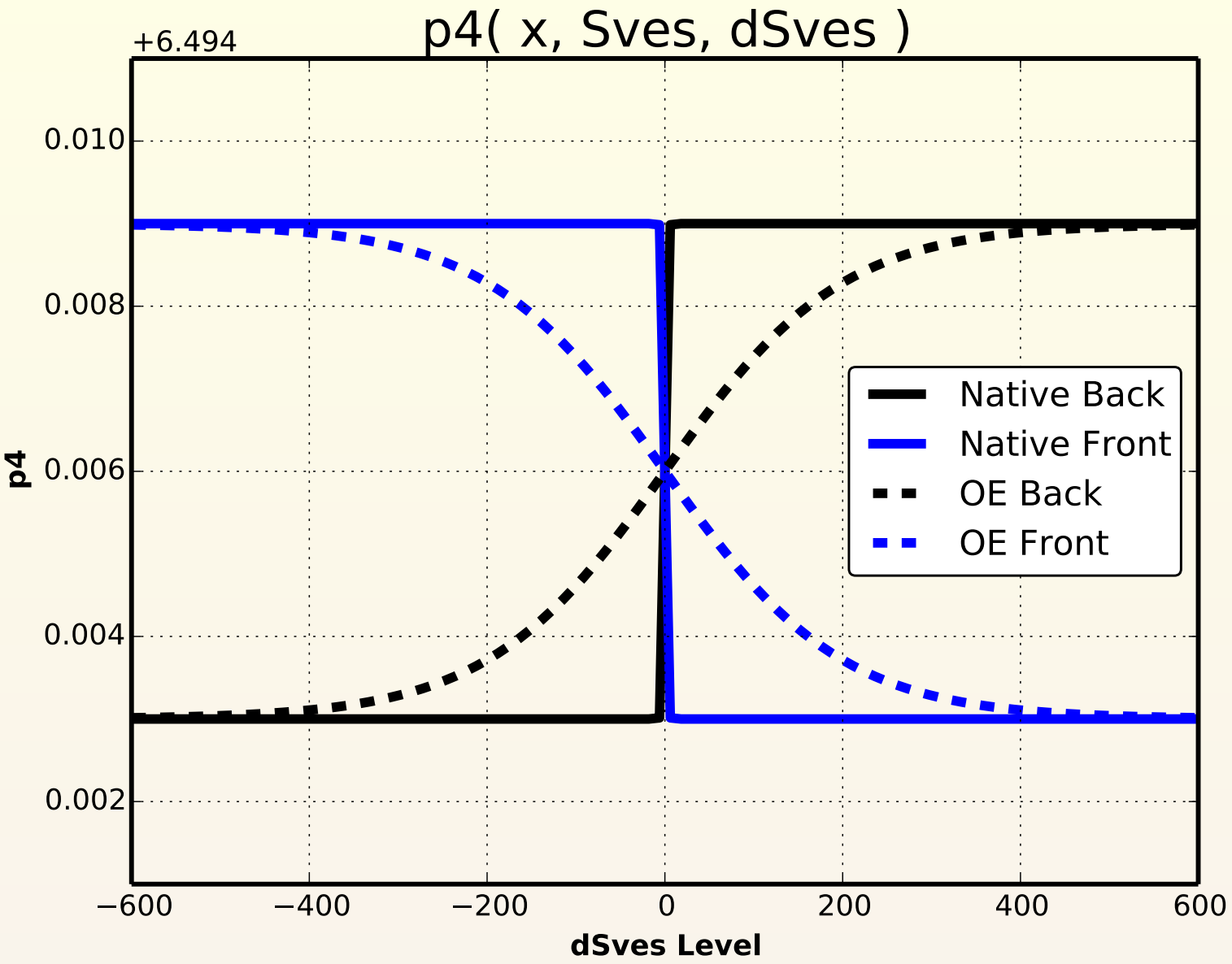

Bell p3
MAPKpp Native
MAPKpp Overexp
MI Native
MI Overexp
MAPKpp
MI
Input
p3
Smem
0.0
0.2
0.4
0.6
0.8
1.0
1.2
−2
0
2
4
6
8
10
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.5
1.5
2.0
2.5
3.0

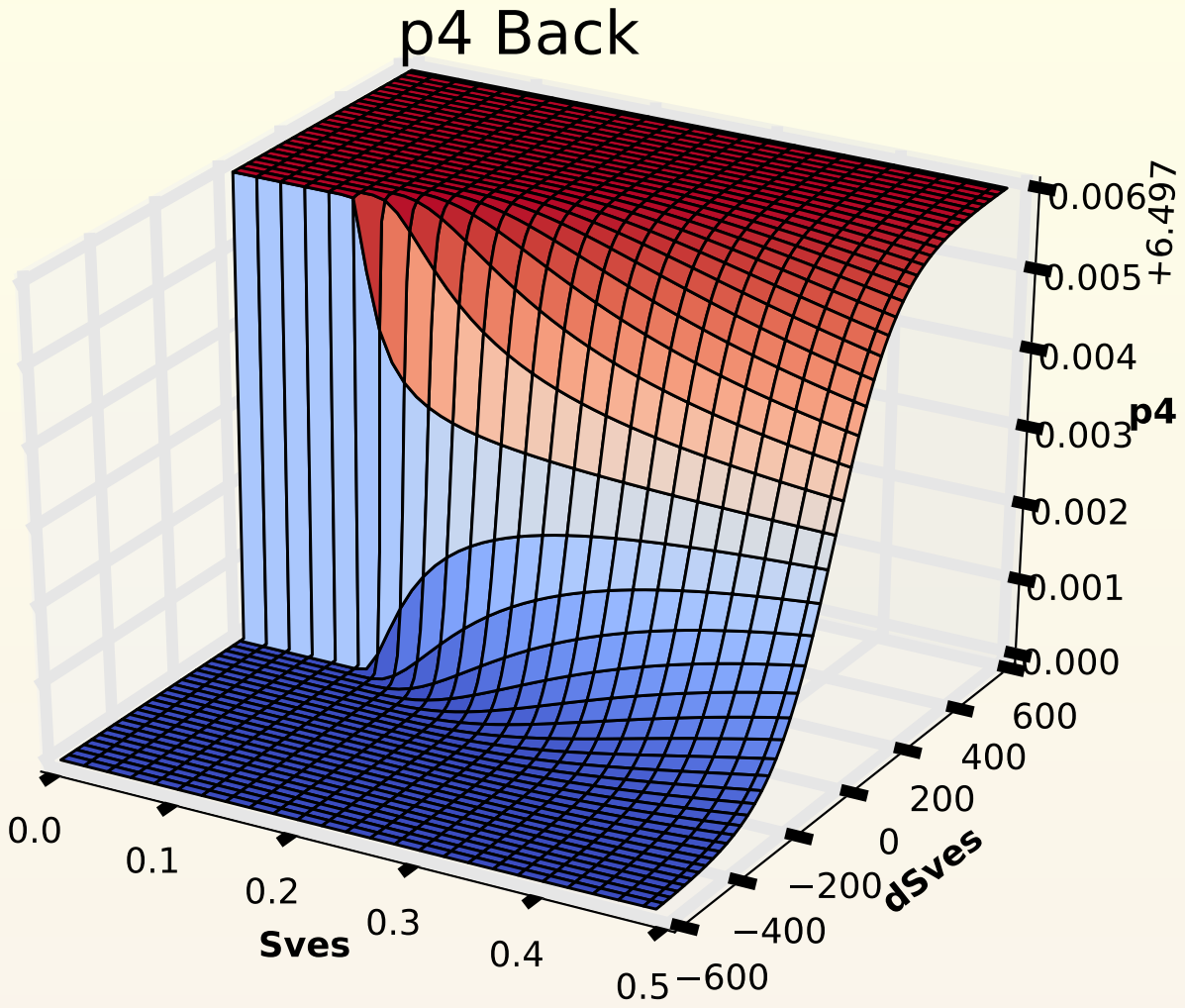
Results for bell shaped p3

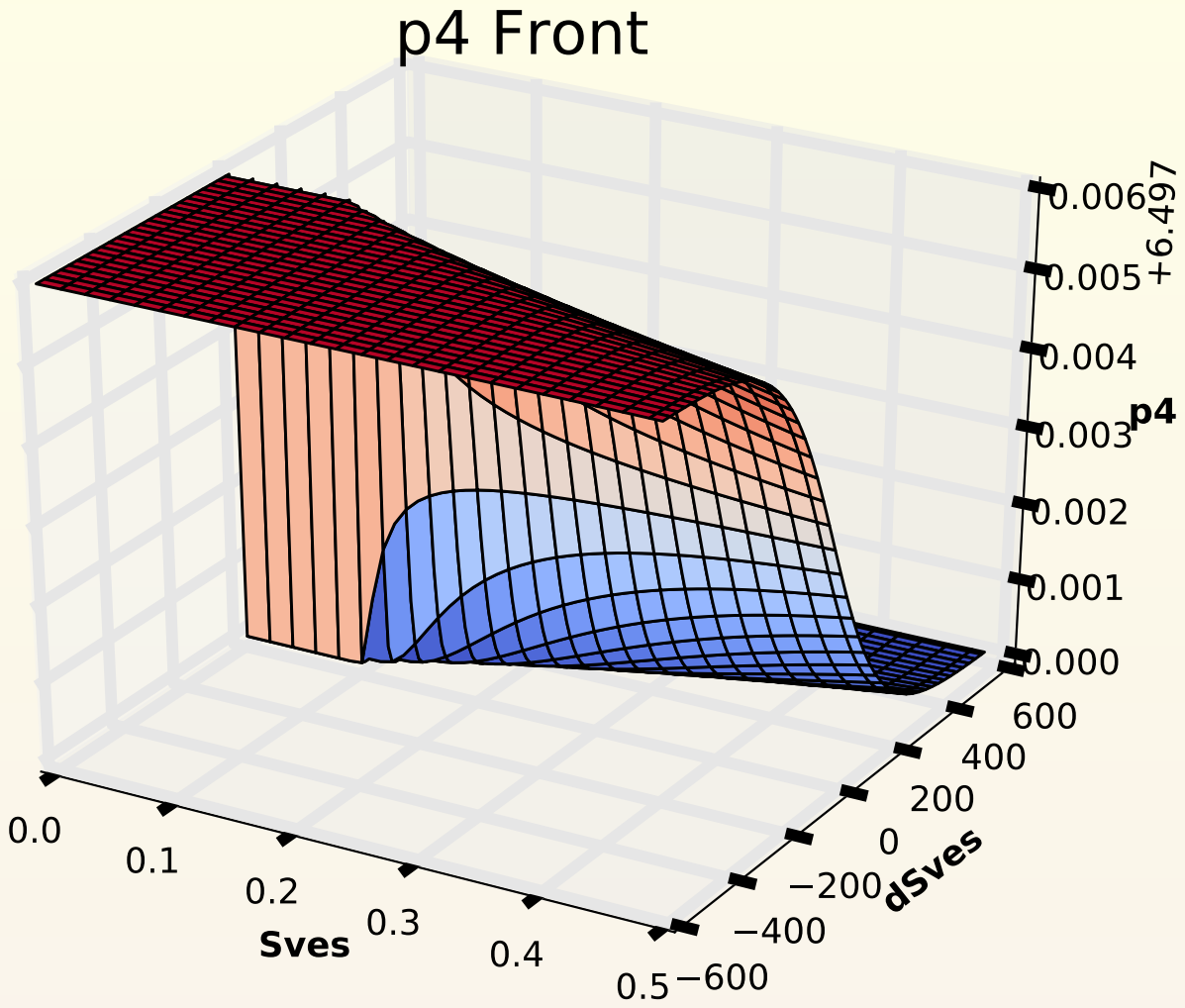
- Now the experimental results can be satisfied at both expression levels
- At native levels, MAPKpp rises linearly, producing constant MI
- At overexpressed levels, MAPKpp has an inverted bell response, producing a MI curve that changes sign

p4 as a function of Sves and dSves

- Previously I've demonstrated why p4 had to be a function of dSves
- dSves serves as the polarity compass btw front and back of the cell
- Now I'm demonstrating why p4 needs to be a function of Sves as well
- Sves serves as sigmoidal strength factor
  - Low Sves: short transition range
  - High Sves: long transition range


p4(x, Sves, dSves)
+6.494
0.010
0.008
0.006
0.004
0.002
p4
−600
−400
−200
0
200
400
600
dSves Level
Native Back
Native Front
OE Back
OE Front

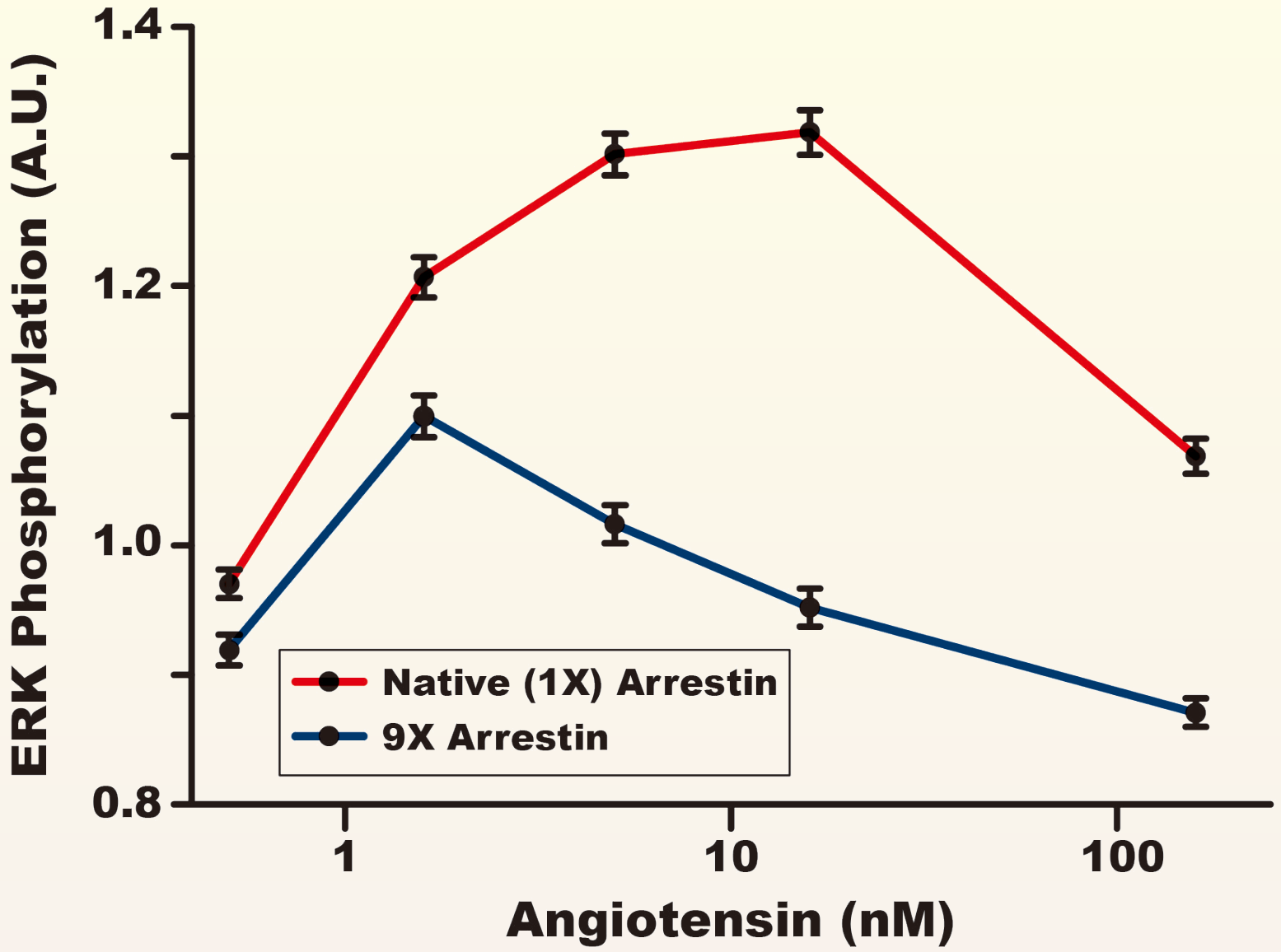

p4 Back
0.006
0.005
0.004
0.003
0.002
0.001
0.000
+6.497
p4
600
400
200
0
−200
−400
−600
dSves
0.0
0.1
0.2
0.3
0.4
0.5
Sves


p4 Front
0.006
0.005
0.004
0.003
0.002
0.001
0.000
+6.497
p4
600
400
200
0
−200
−400
−600
dSves
0.0
0.1
0.2
0.3
0.4
0.5
Sves

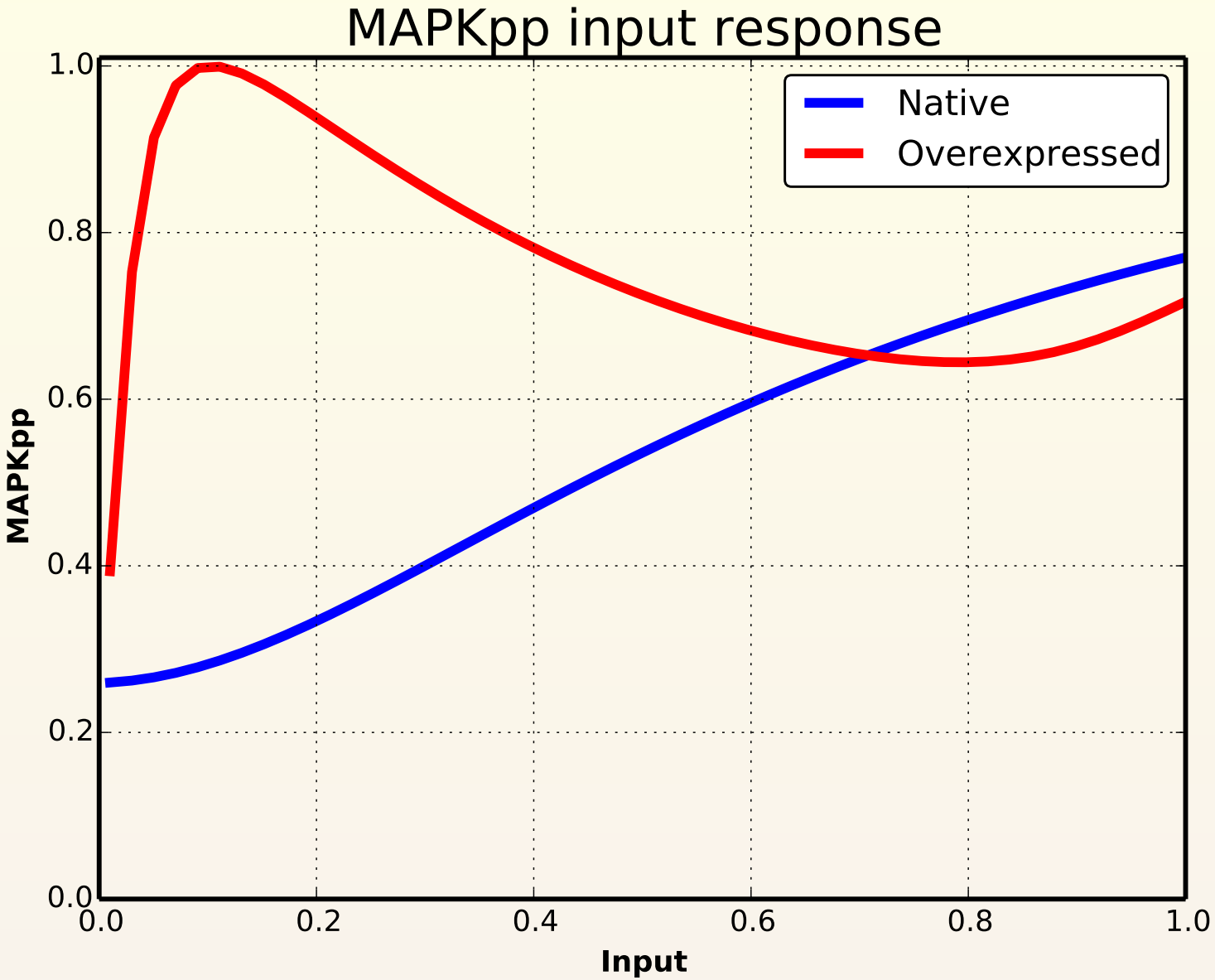
Comparison with experiments

MAPKpp Dose Response

D

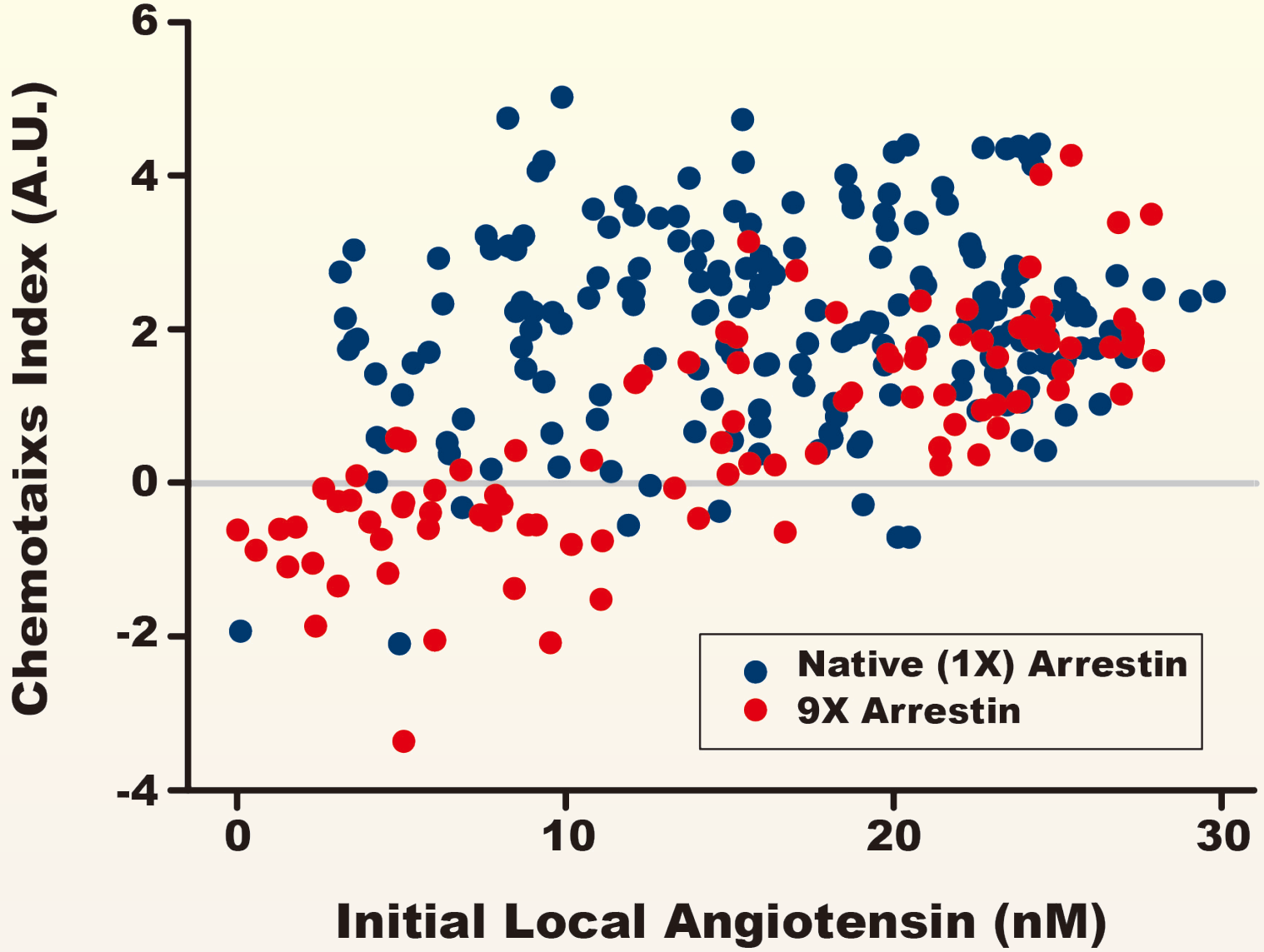


MAPKpp Dose Response

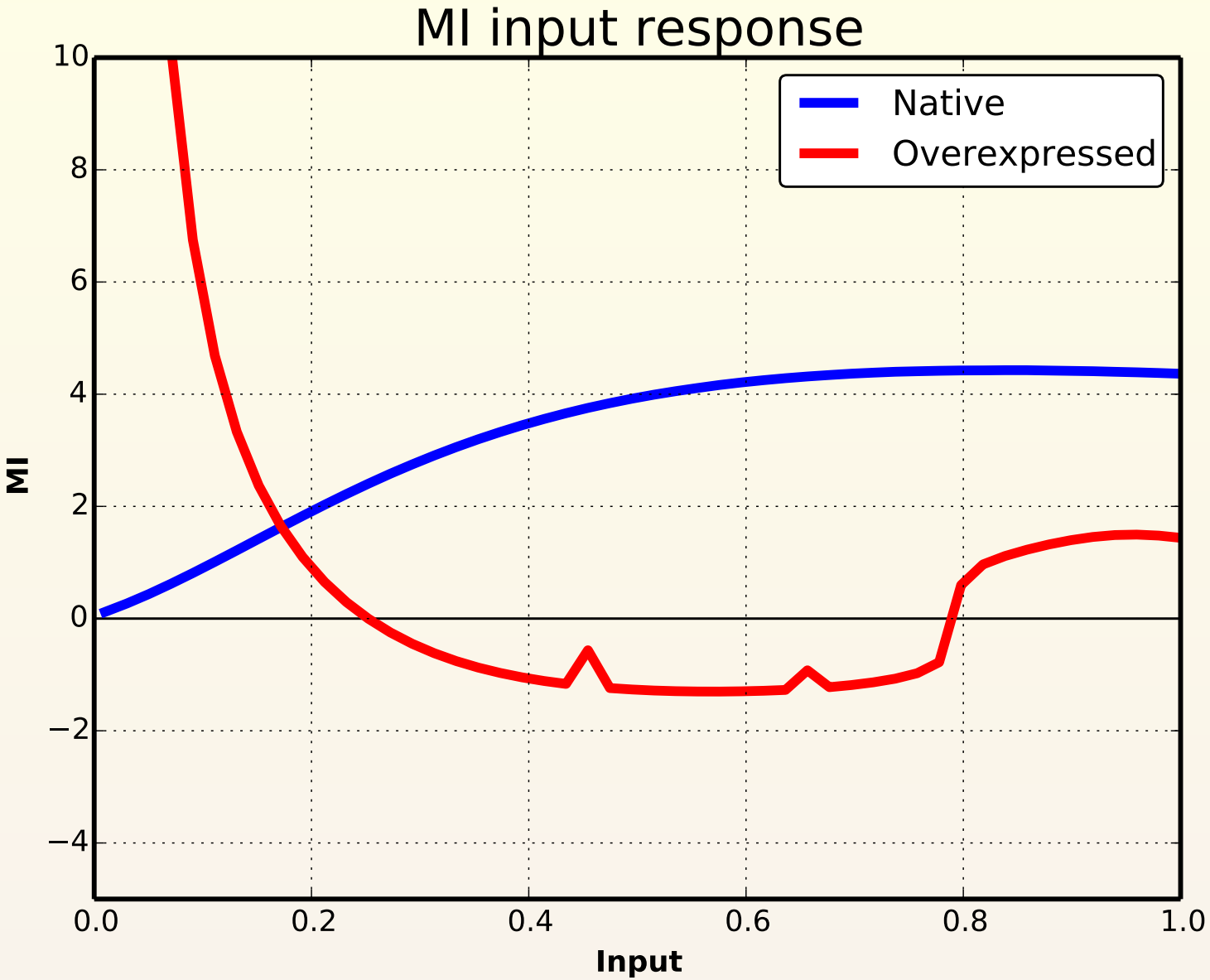


MI Dose Response

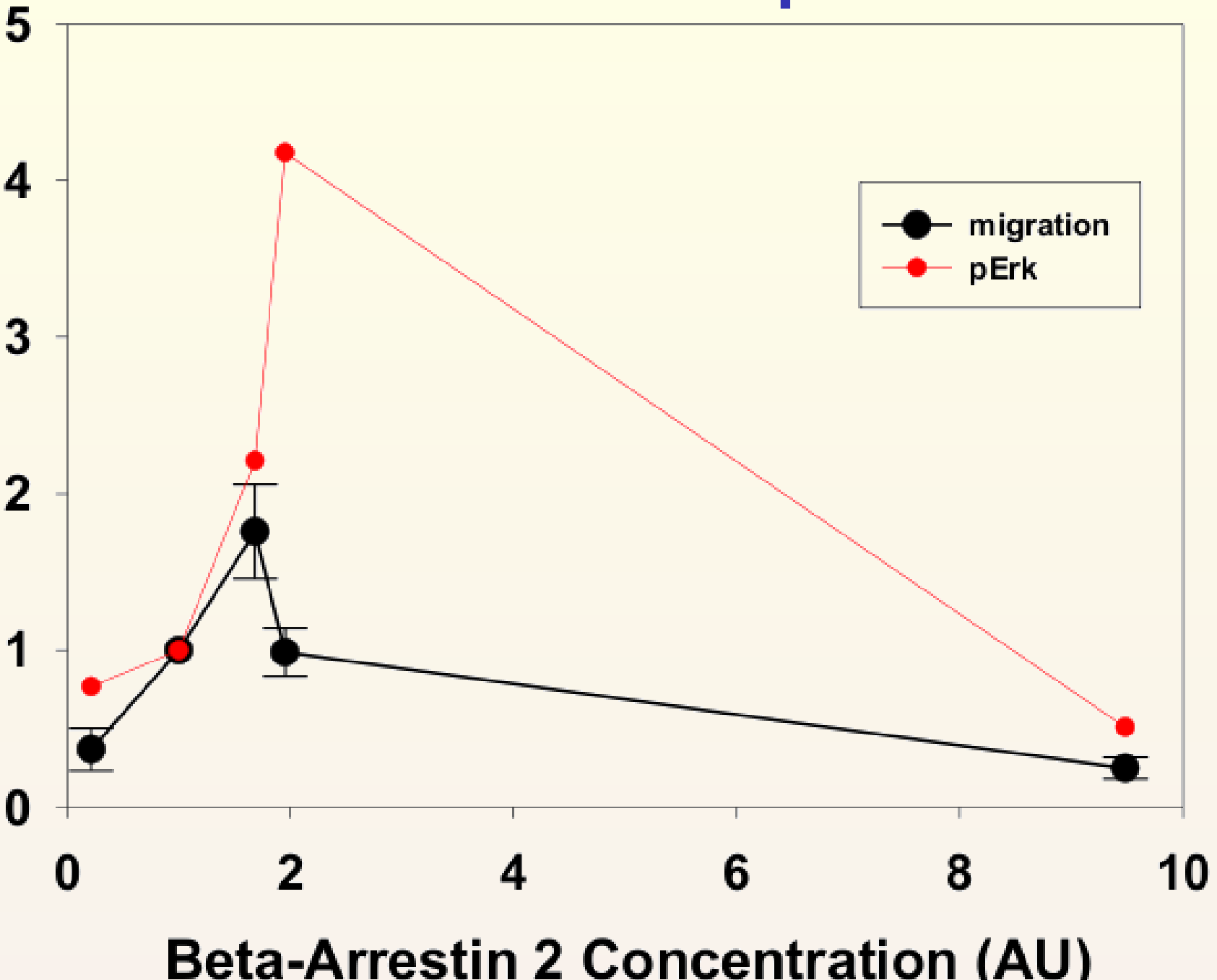
B



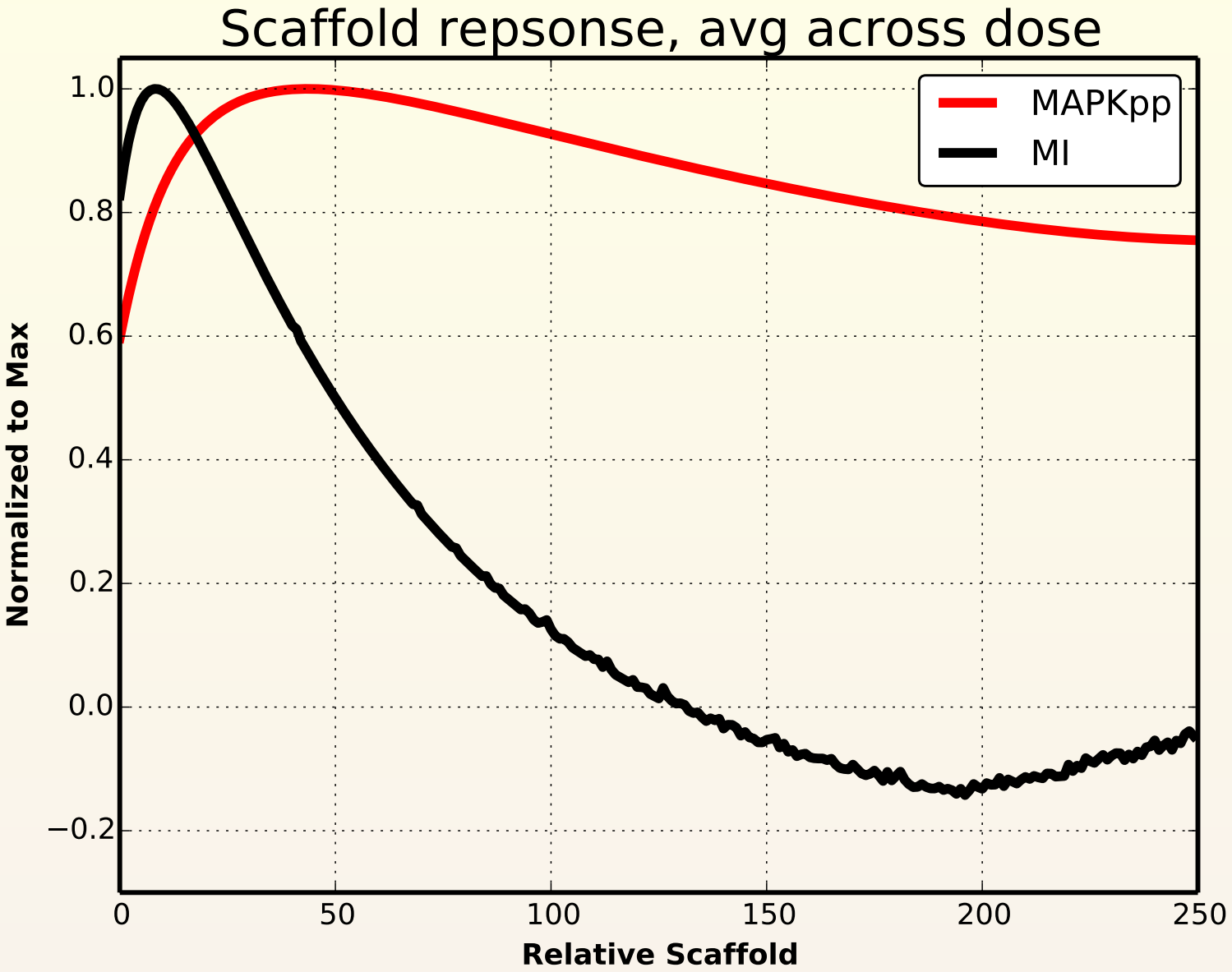
MI Dose Response



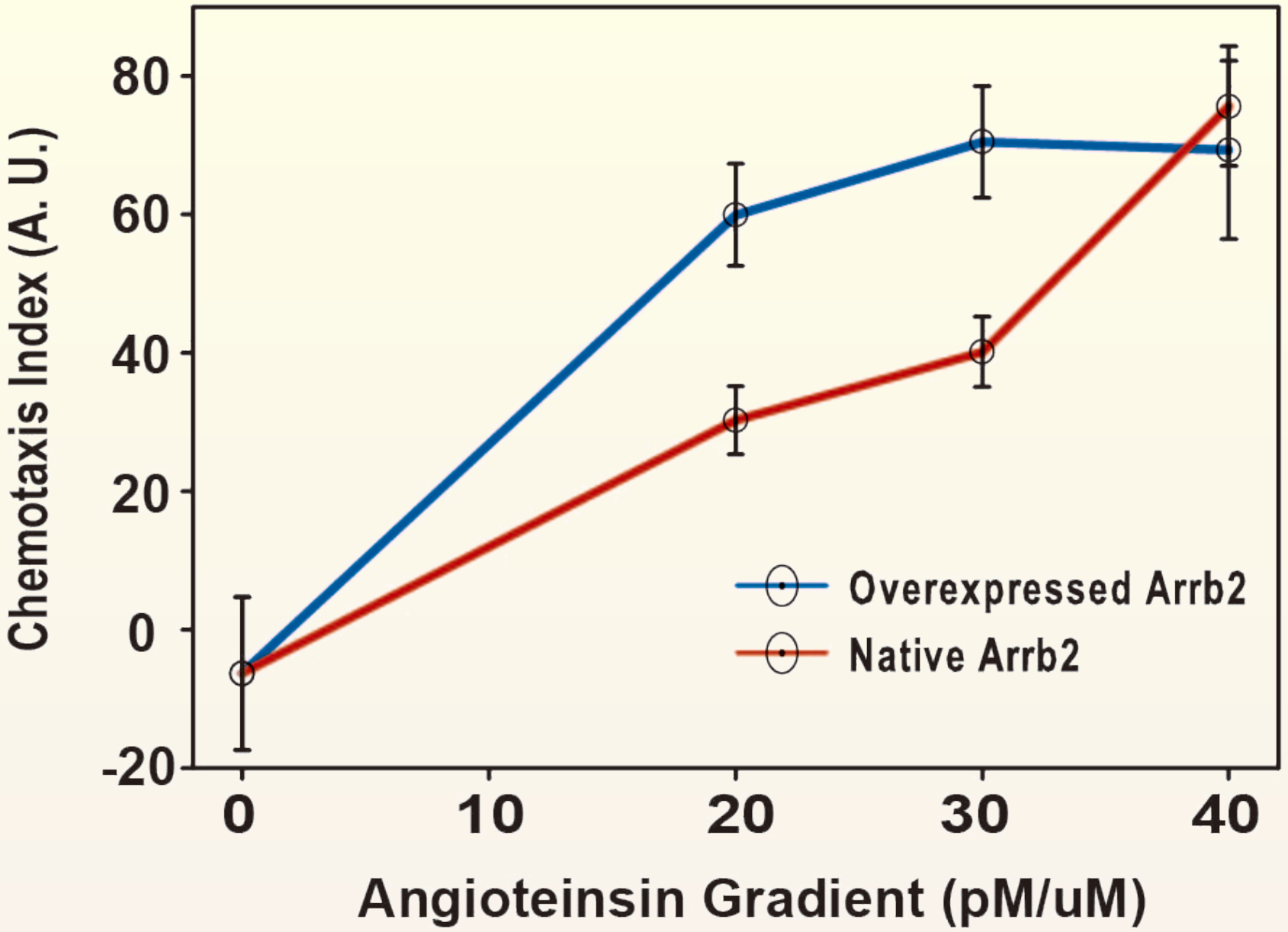
Scaffold Response



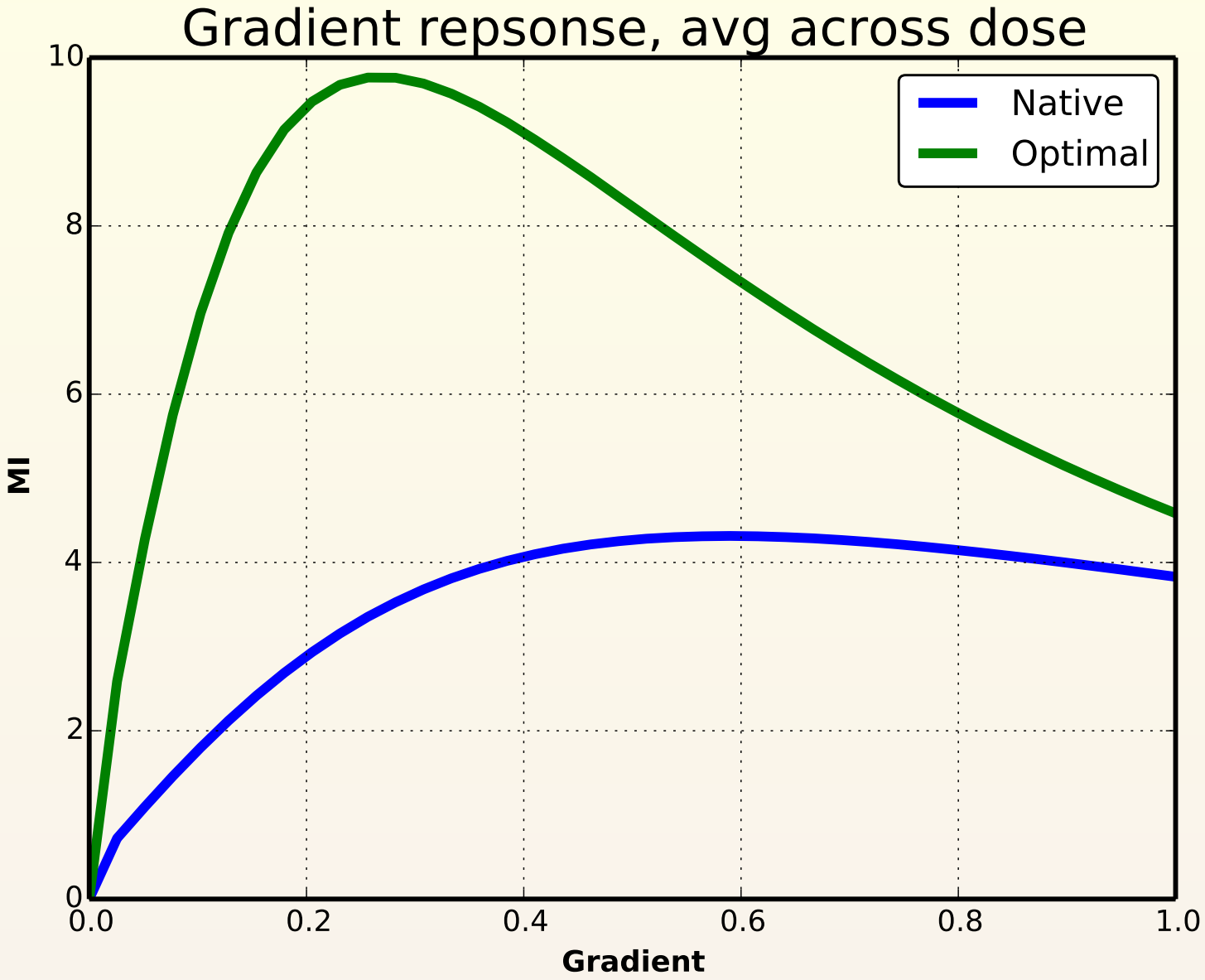
Scaffold Response



Gradient Response

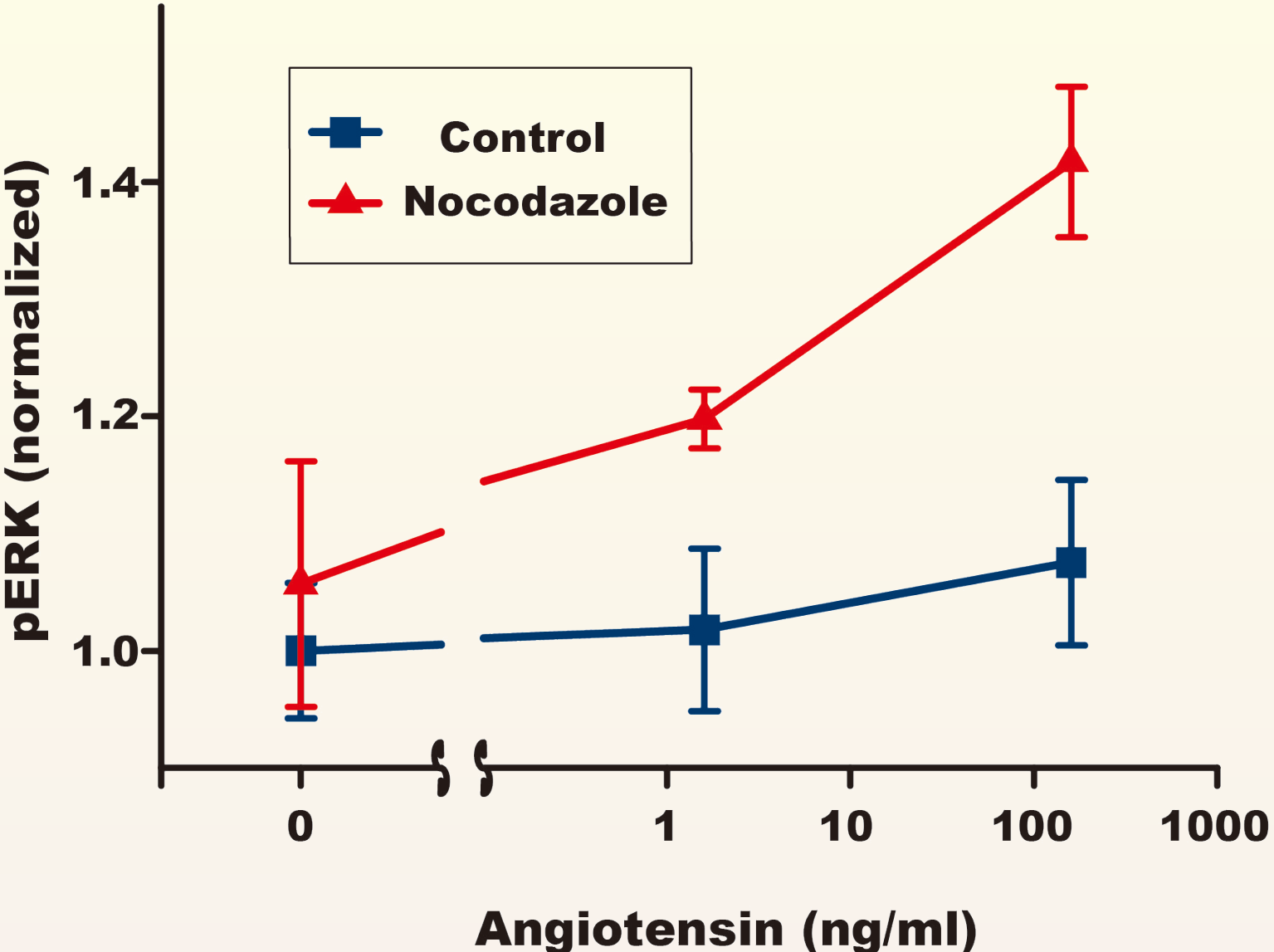


Gradient Response

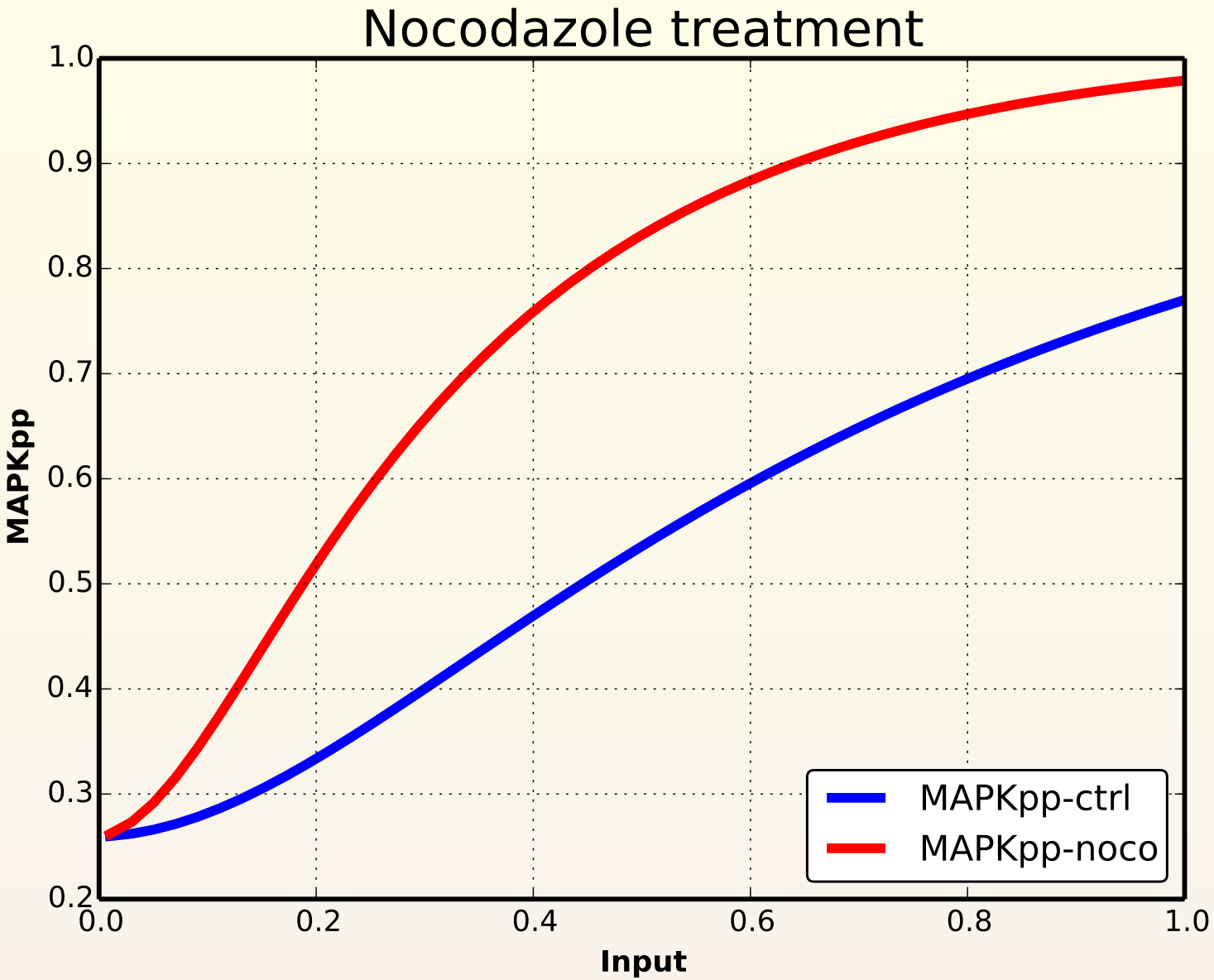


Nocodazole treatment

E

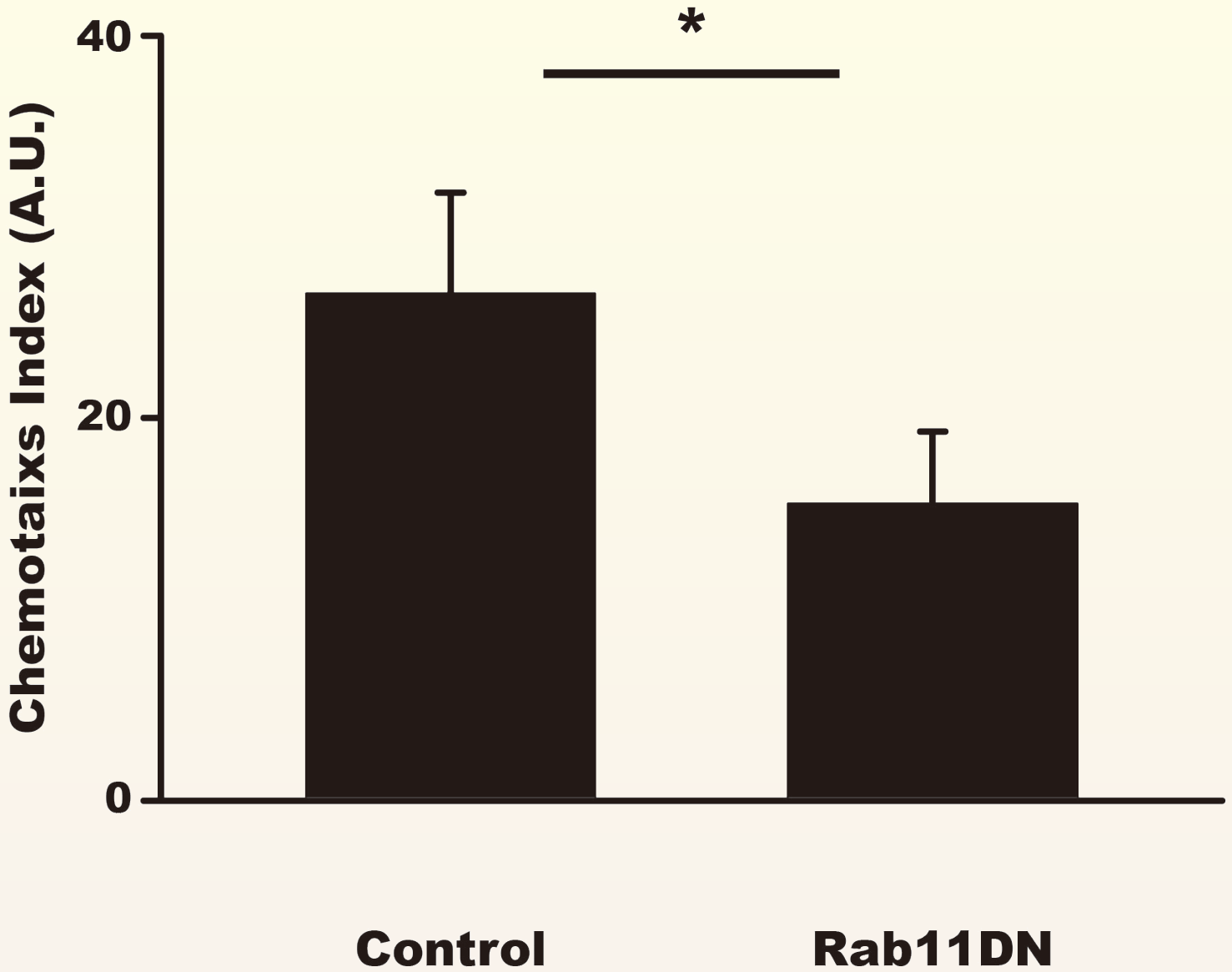


$S_{ves} \rightarrow S_{cyto}, 20\% p_4$



Rab11-DN

F



Rab11-DN