Study of Tricyclic Cascade Networks using Dynamic Optimization

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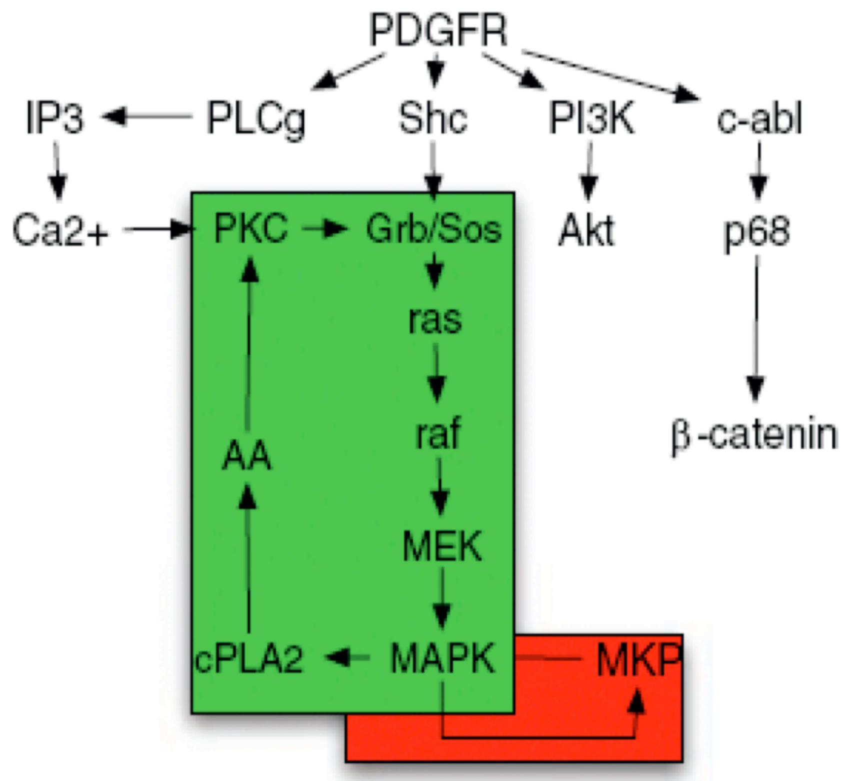
Background and Scope

- **Systems Biology** – interdisciplinary field that focuses on the systematic study of complex interactions in biological systems

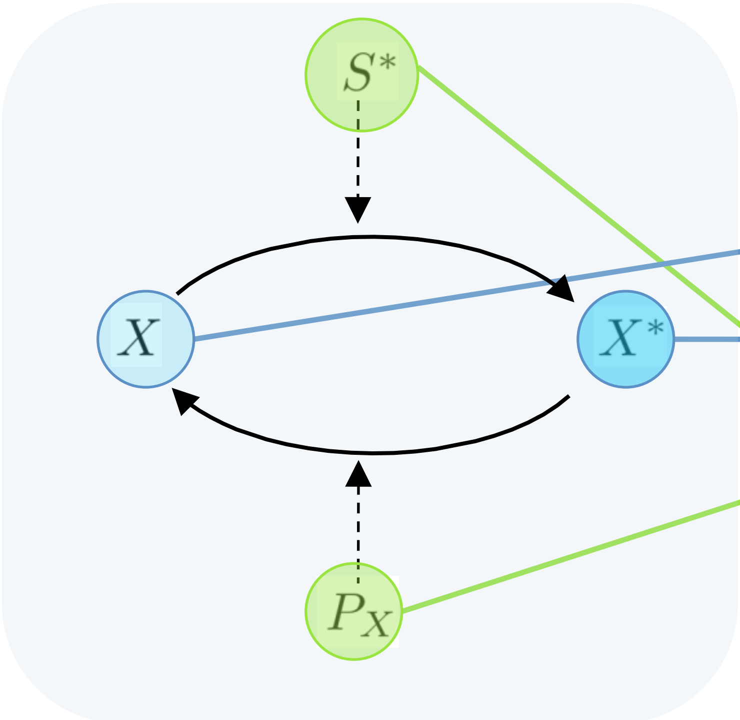
- **Signal transduction pathways**
  - enable cells to integrate external and internal signals and to respond to them,
  - are present in major developmental changes in organism (embryo development, but also in cancer, asthma, diabetes…)



H. Kestler, C. Wawra, B. Kracher and M. Kuhl:
"Network modeling of signal transduction: establishing the global view".
Bioessays. 30:1110-1125. 2008

Signaling Cascade

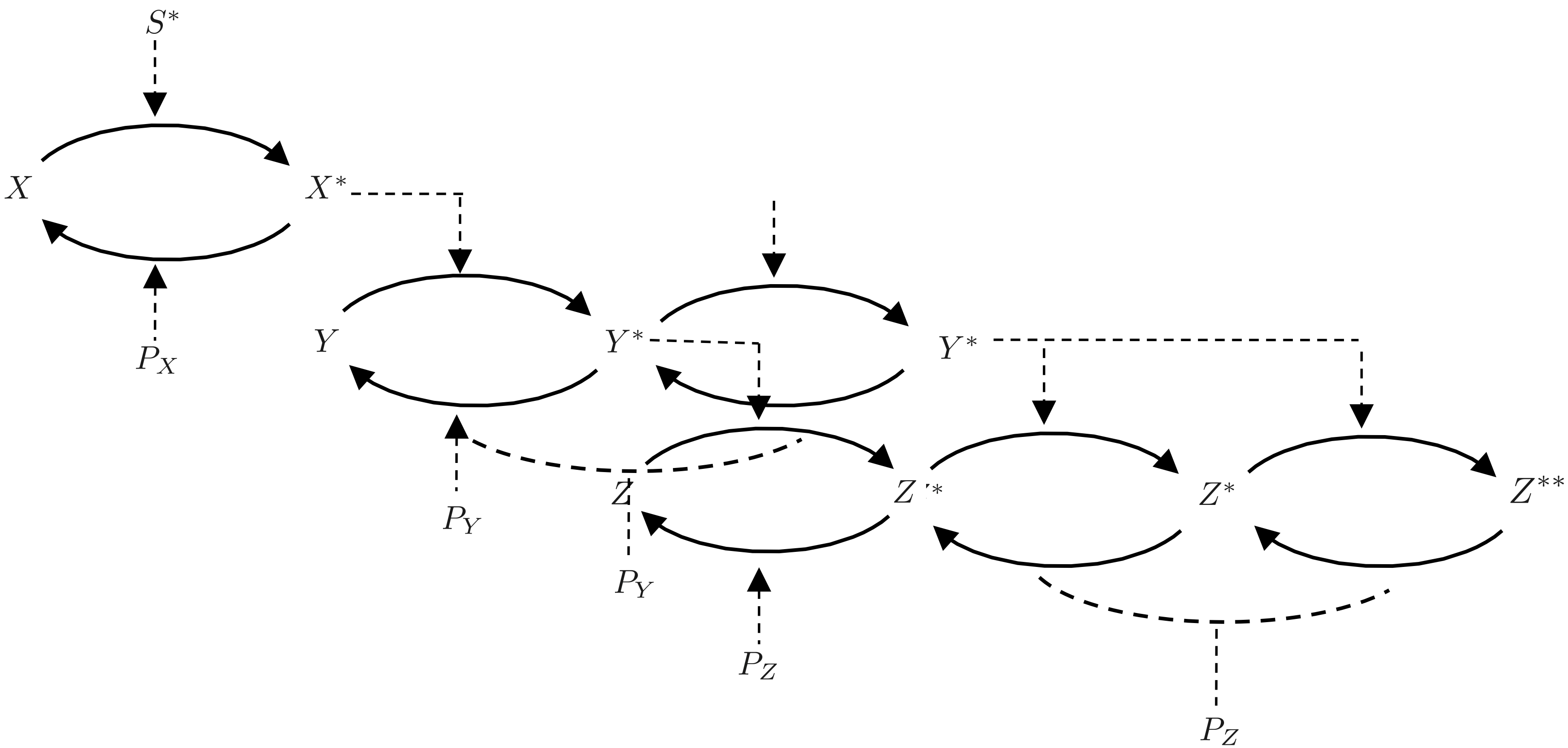
- Basic module



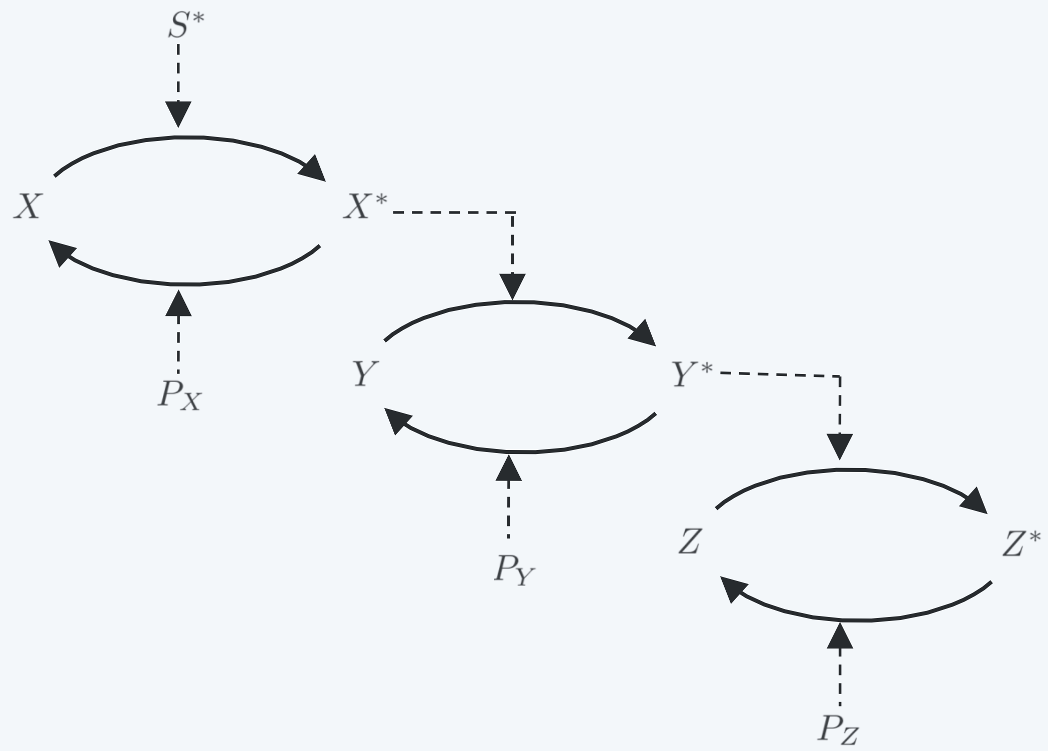
- Protein
  - Inactive - X
  - Active – X*
- Enzymes – S* and P_X

- phosphorylation/dephosphorylation in MAPK cascades
- methylation/demethylation in bacterial chemotaxis

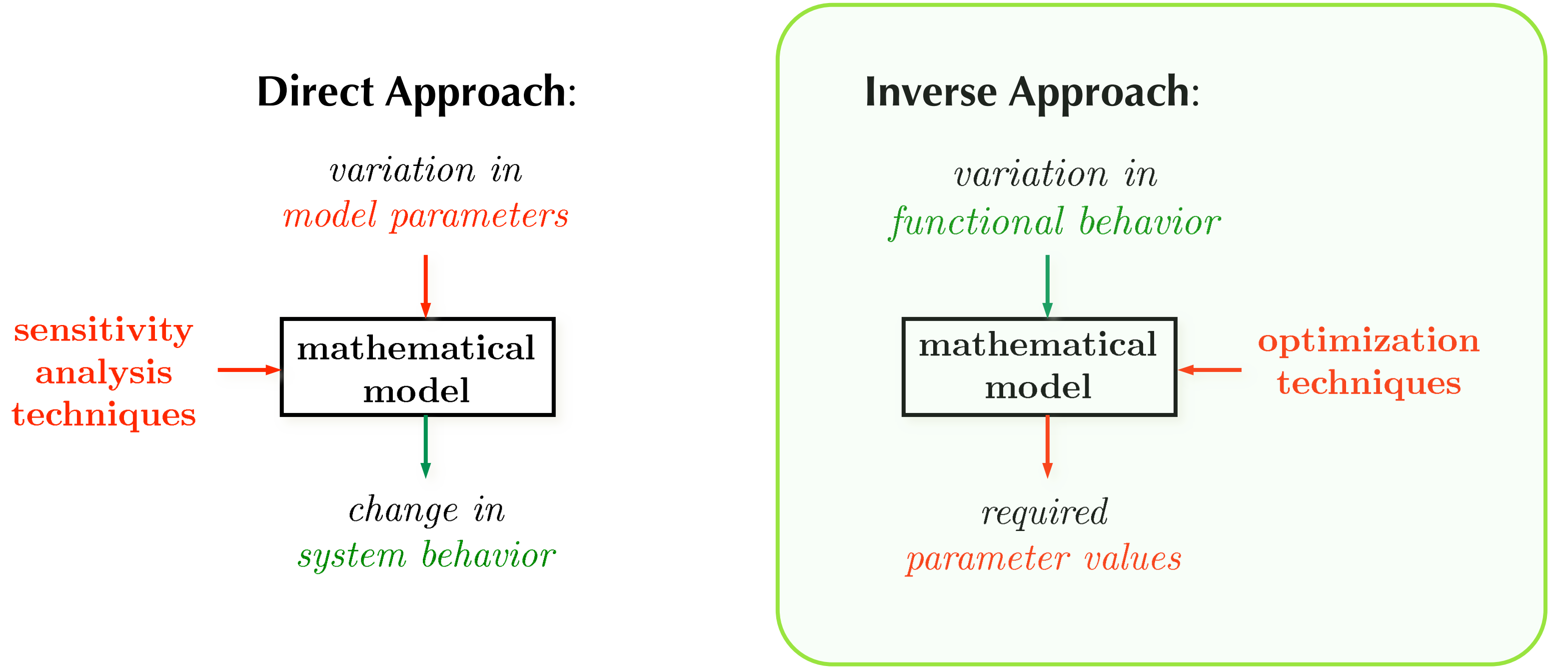
Signaling Cascade



Signaling Cascade



Methodology

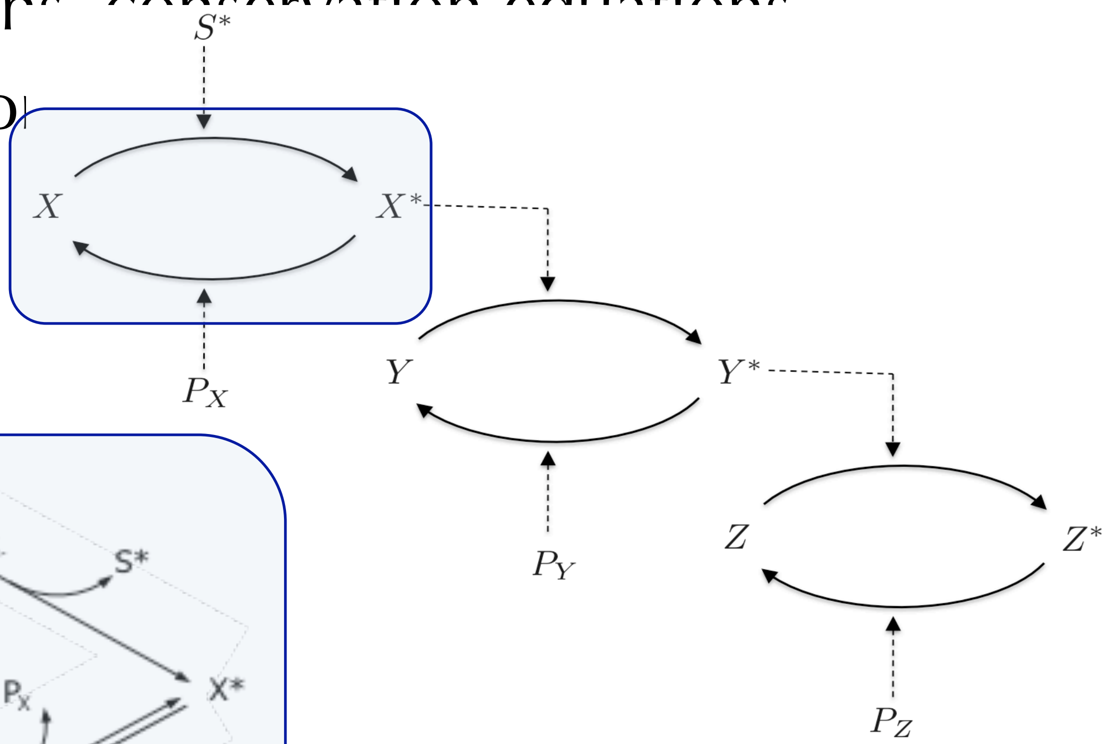


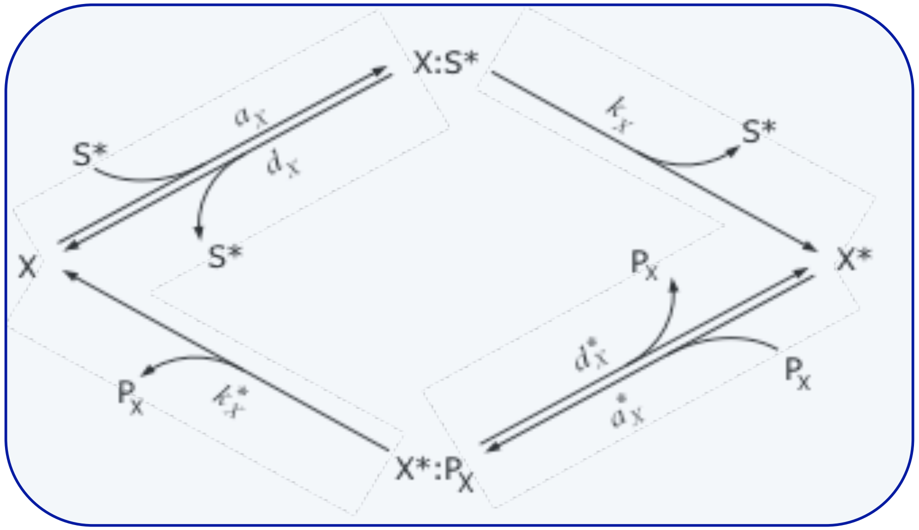
Both *direct* and *inverse* approaches work synergistically!

- **Dynamic optimization**
  - very well suited for studying biochemical networks
  - it allows dealing with large-scale, nonlinear dynamic models
  - can handle a great variety of objective functions and constraints.

Monocyclic Cascade: Mathematical Model

- balance equations, conservation equations
- kinetic expressio





Monocyclic Cascade: Mathematical Model

- balance equations, conservation equations
- kinetic expressions

$$[X]_{tot} = [X] + [X^*] + [X:S^*] + [X^*:P_X]$$

$$[S]_{tot} = [S] + [S^*] + [X:S^*]$$

$$[P_X]_{tot} = [P_X] + [X^*:P_X]$$

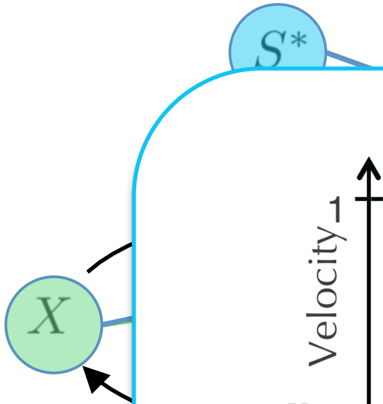
$$\frac{\mathrm{d}[X^*]}{\mathrm{d}t} = -a_X^*[X^*][P_X] + d_X^*[X^*:P_X] + k_X[X:S^*]$$

$$\frac{\mathrm{d}[X:S^*]}{\mathrm{d}t} = a_X[X][S^*] - (d_X + k_X)[X:S^*]$$

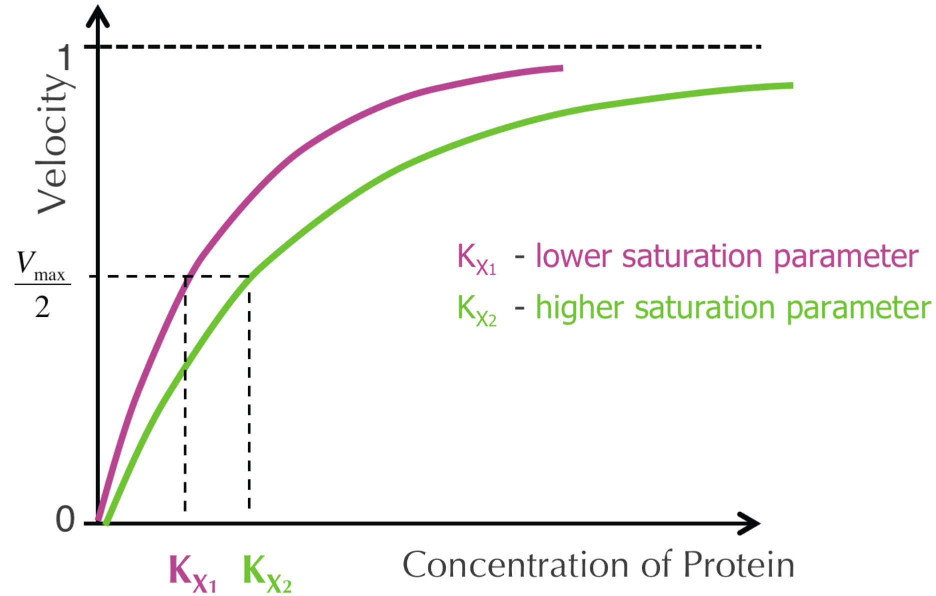
$$\frac{\mathrm{d}[X^*:P_X]}{\mathrm{d}t} = a_X^*[X^*][P_X] - (d_X^* + k_X^*)[X^*:P_X]$$

- Kinetic parameters: $\tilde{a}_X, \tilde{a}_X^*, \tilde{d}_X, \tilde{d}_X^*, \tilde{k}_X$

Key System Parameters



- Concentration ratios

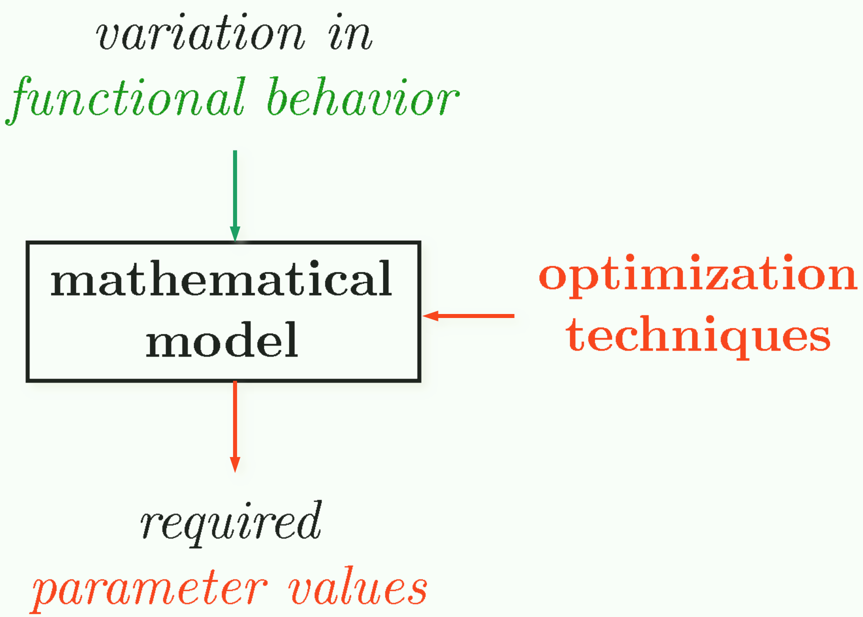


$$= \frac{\tilde{d}_X^* + 1}{\tilde{a}_X^*}$$

$$\alpha_X := \tilde{k}_X \frac{\rho^{S/X}}{\rho^{P_X/X}}$$

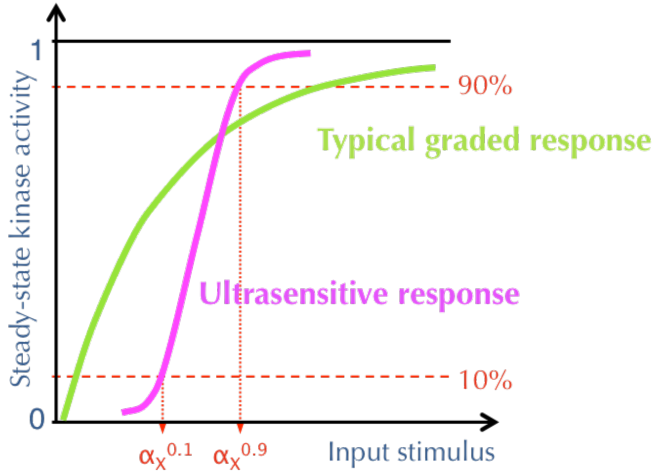
Methodology

Inverse Approach:

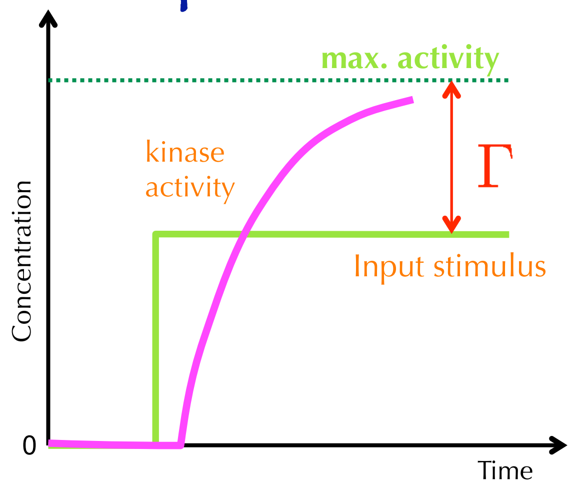


Design Objectives

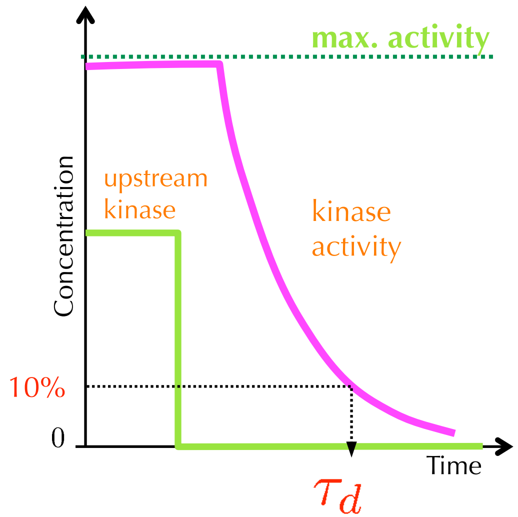
Ultrasensitivity

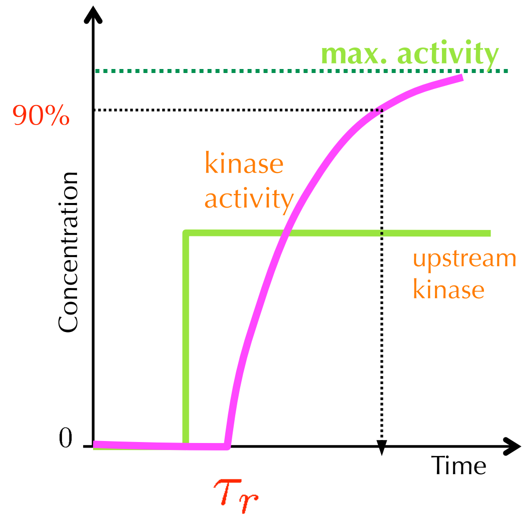


Amplification:

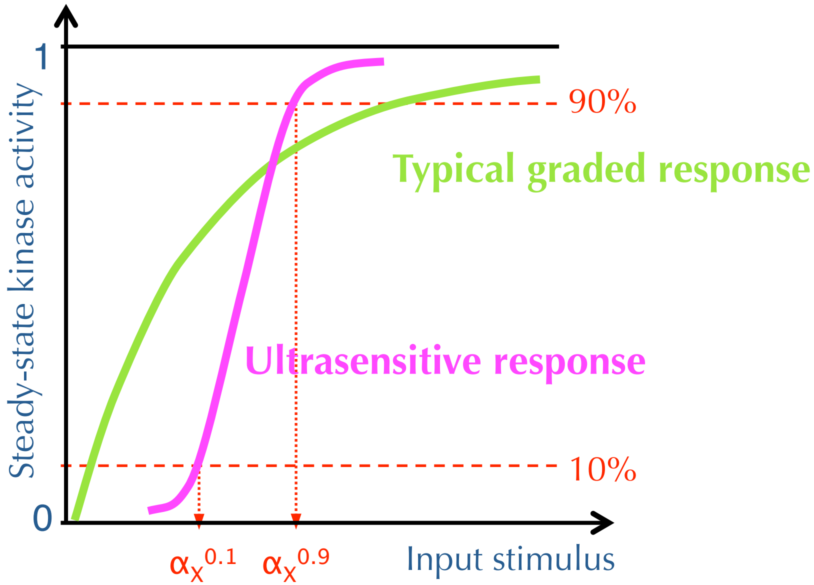


Signal propagation times





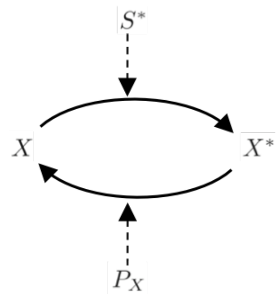
Design Objective: Ultrasensitivity



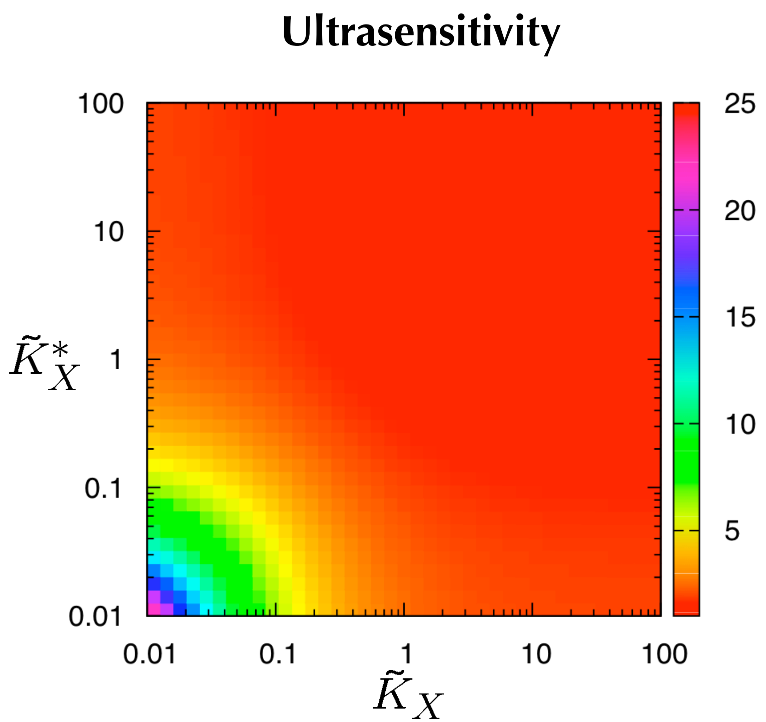
- Go from a typical graded response to a switch-like response

$$n_H := \frac{\ln(81)}{\ln(\alpha_X^{0.9}) - \ln(\alpha_X^{0.1})}$$

Results: Monocyclic Cascade

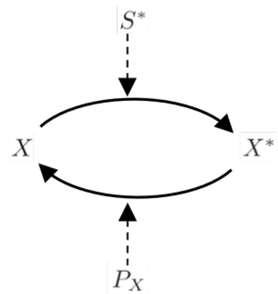


- Optimal ultrasensitivity for fixed values of ratios between total concentrations of enzymes and substrate:

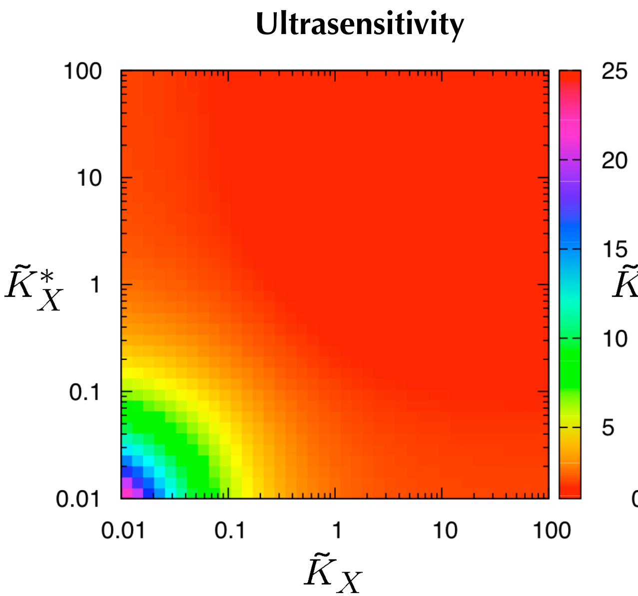


[S]/[X] = 0.01

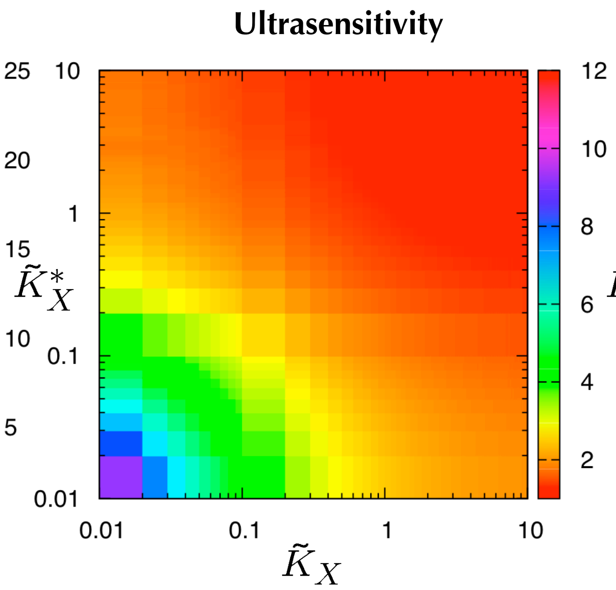
Results: Monocyclic Cascade



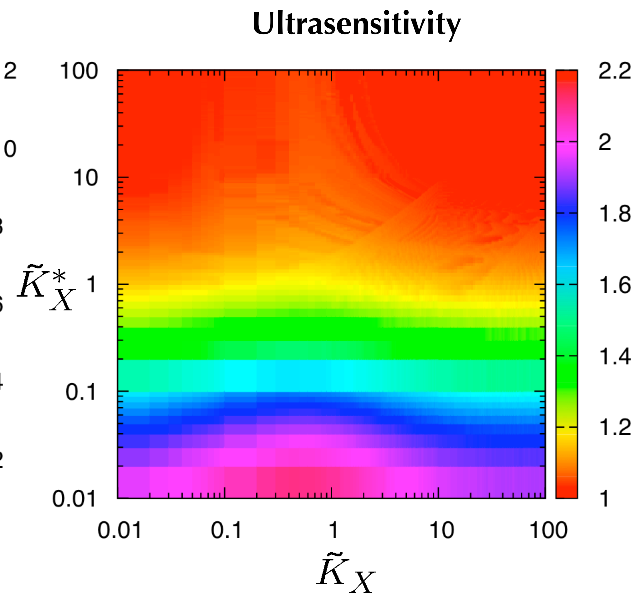
- Optimal ultrasensitivity for fixed values of ratios between total concentrations of enzymes and substrate:



[S]/[X] = 0.01

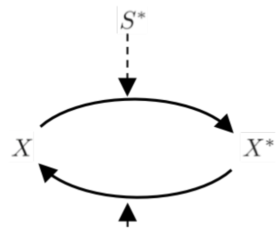


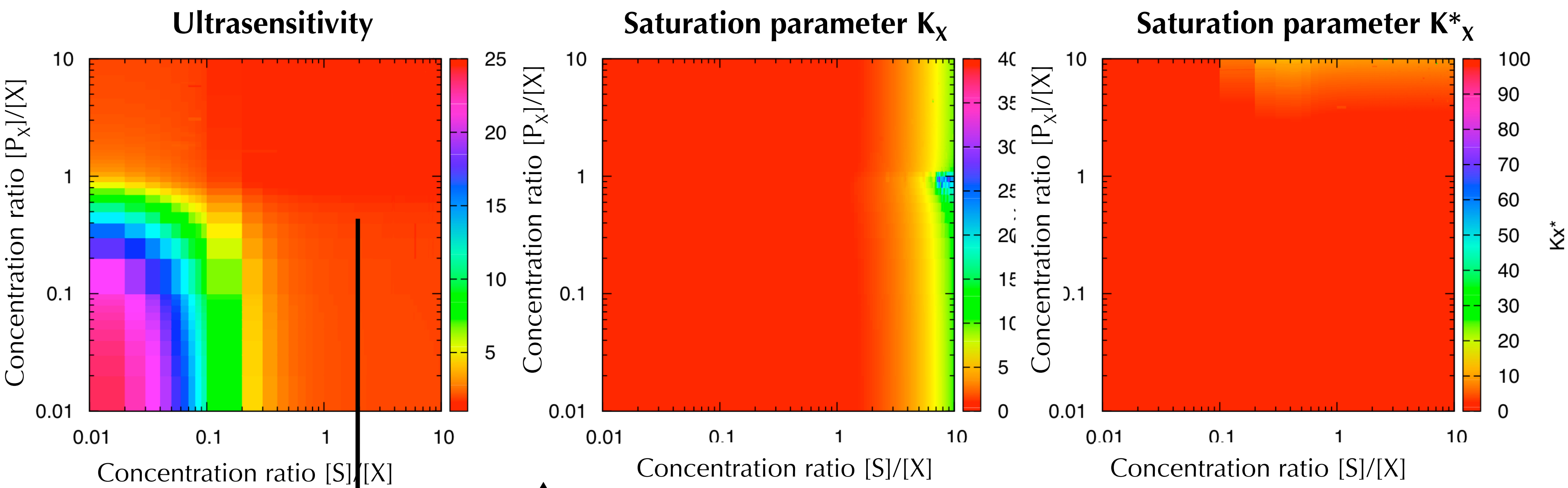
[S]/[X] = 0.1

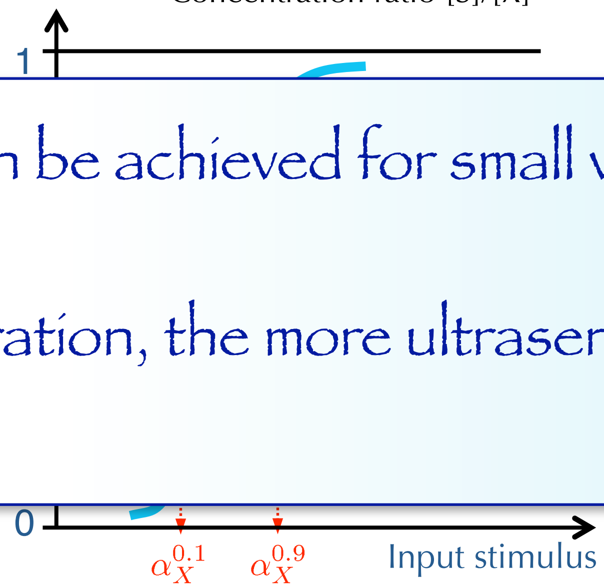


[S]/[X] = 1

Results: Monocyclic Cascade







- ✓ Ultrasensitivity can be achieved for small values of concentration ratios
- ✓ The closer to saturation, the more ultrasensitive the monocyclic cascade.

Bicyclic Cascade:
Mathematical Model

$$[X]_{tot} = [X] + [X^*] + [X:S^*] + [X^*:P_X] + [Y:X^*]$$

$$[S]_{tot} = [S] + [S^*] + [X:S^*]$$

$$[P_X]_{tot} = [P_X] + [X^*:P_X]$$

$$\frac{\mathrm{d}[X^*]}{\mathrm{d}t} = -a_X^*[X^*][P_X] + d_X^*[X^*:P_X] + k_X[X:S^*] - a_Y[Y][X^*] + (d_Y + k_Y)[Y:X^*]$$

$$\frac{\mathrm{d}[X:S^*]}{\mathrm{d}t} = a_X[X][S^*] - (d_X + k_X)[X:S^*]$$

$$\frac{\mathrm{d}[X^*:P_X]}{\mathrm{d}t} = a_X^*[X^*][P_X] - (d_X^* + k_X^*)[X^*:P_X]$$

$$[Y]_{tot} = [Y] + [Y^*] + [Y:X^*] + [Y^*:P_Y]$$

$$[P_Y]_{tot} = [P_Y] + [Y^*:P_Y]$$

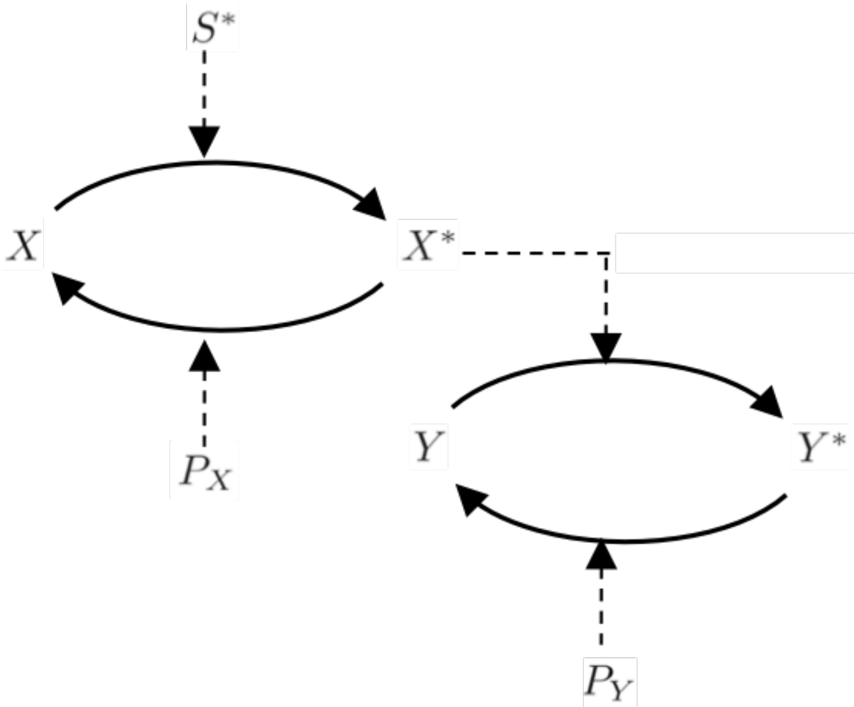
$$\frac{\mathrm{d}[Y^*]}{\mathrm{d}t} = -a_Y^*[Y^*][P_Y] + d_Y^*[Y^*:P_Y] + k_Y[Y:X^*]$$

$$\frac{\mathrm{d}[Y:X^*]}{\mathrm{d}t} = a_Y[Y][X^*] - (d_Y + k_Y)[Y:X^*]$$

$$\frac{\mathrm{d}[Y^*:P_Y]}{\mathrm{d}t} = a_Y^*[Y^*][P_Y] - (d_Y^* + k_Y^*)[Y^*:P_Y]$$

- Kinetic parameters: $\tilde{a}_{X,}, \tilde{a}_X^*, \tilde{d}_X, \tilde{d}_X^*, \tilde{k}_X, \tilde{a}_Y, \tilde{a}_Y^*, \tilde{d}_Y, \tilde{d}_Y^*, \tilde{k}_Y, \tilde{k}_Y^*$

Key System Parameters



- Concentration ratios

$$\rho^{S/X}, \rho^{P_X/X}, \rho^{X/Y}, \rho^{P_Y/Y}$$

- Saturation parameters

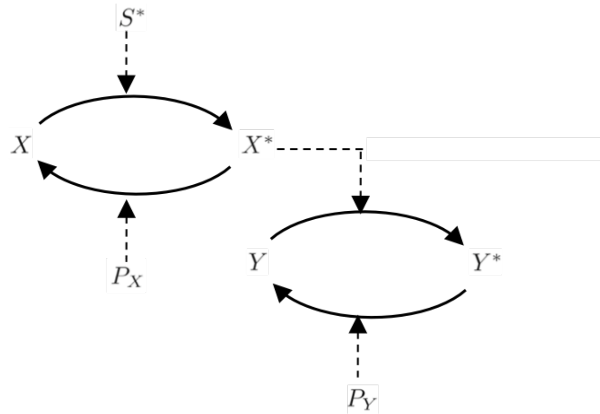
$$\tilde{K}_X = \frac{\tilde{d}_X + \tilde{k}_X}{\tilde{a}_X} \qquad \tilde{K}_X^* = \frac{\tilde{d}_X^* + 1}{\tilde{a}_X^*}$$

$$\tilde{K}_Y = \frac{\tilde{d}_Y + \tilde{k}_Y}{\tilde{a}_Y} \qquad \tilde{K}_Y^* = \frac{\tilde{d}_Y^* + \tilde{k}_Y^*}{\tilde{a}_Y^*}$$

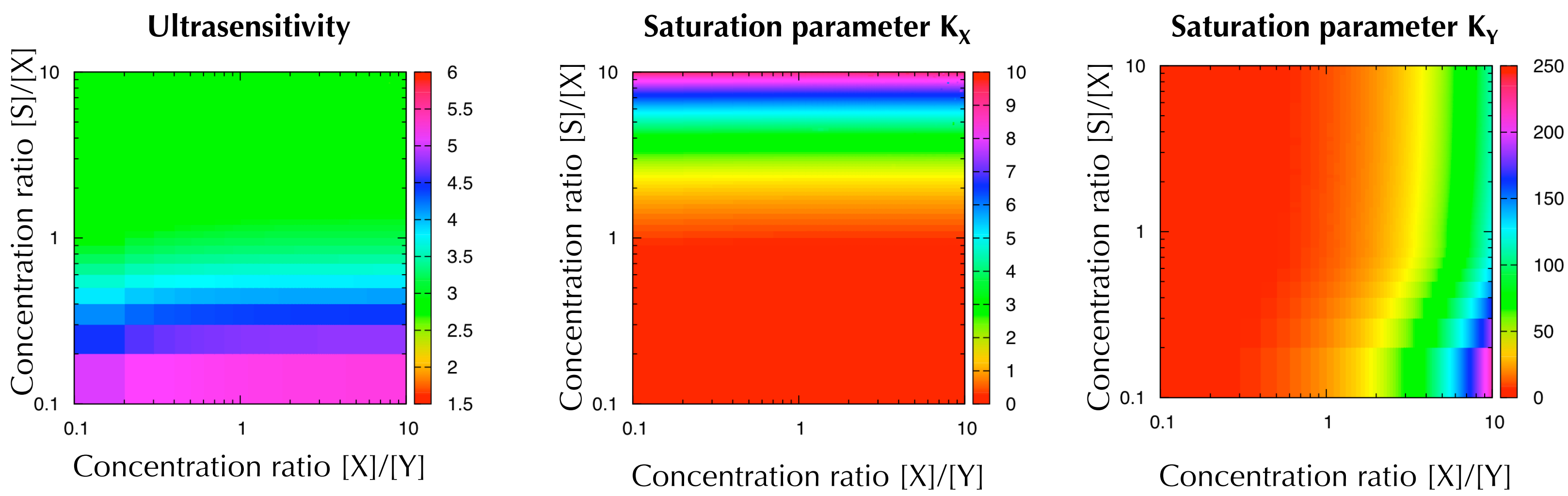
- Activity coefficients

$$\alpha_X = \tilde{k}_X \frac{\rho^{S/X}}{\rho^{P_X/X}} \qquad \alpha_Y = \frac{\tilde{k}_Y}{\tilde{k}_Y^*} \frac{\rho^{X/Y}}{\rho^{P_Y/Y}}$$

Results: Bicyclic Cascade



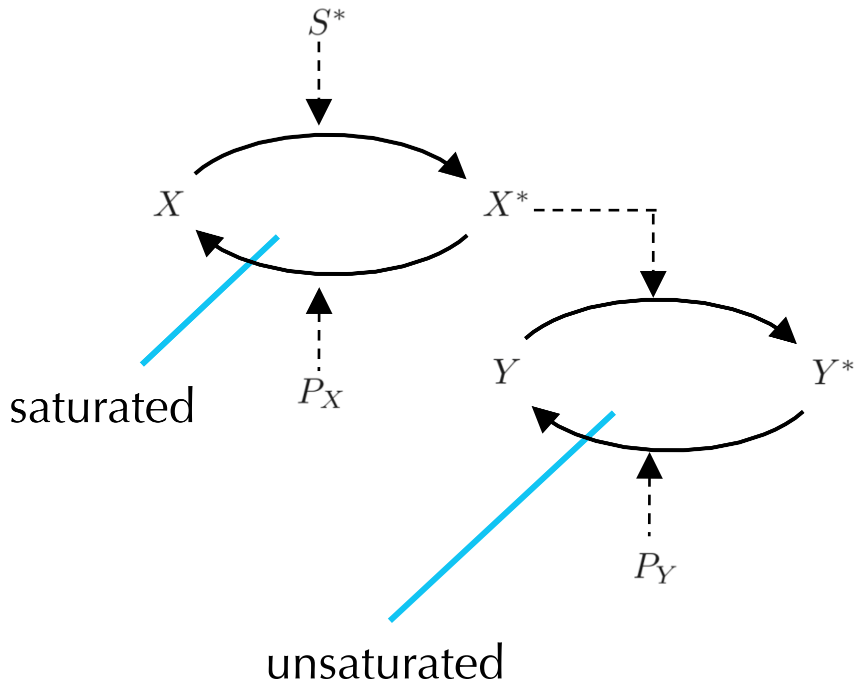
Maximal values of ultrasensitivity objective measure, with corresponding values of saturation parameters for activation reaction of each level in a signaling cascade model:



$$\rho^{P_X/X} = \rho^{P_Y/Y} = 0.01$$

$$\tilde{K}_X^* = \tilde{K}_Y^* = 0.01$$

Results: Bicyclic Cascade



✓ Maximum ultrasensitivity when the first kinase is saturated, but not the second kinase

✓ An optimal multicycle cascade does not correspond to a series of optimal monocyclic cascades

Tricyclic Cascade: Mathematical Model

$$[X]_{tot} = [X] + [X^*] + [X:S^*] + [X^*:P_X] + [Y:X^*]$$

$$[S]_{tot} = [S] + [S^*] + [X:S^*]$$

$$[P_X]_{tot} = [P_X] + [X^*:P_X]$$

$$\frac{\mathrm{d}[X^*]}{\mathrm{d}t} = -a_X^*[X^*][P_X] + d_X^*[X^*:P_X] + k_X[X:S^*] - a_Y[Y][X^*] + (d_Y + k_Y)[Y:X^*]$$

$$\frac{\mathrm{d}[X:S^*]}{\mathrm{d}t} = a_X[X][S^*] - (d_X + k_X)[X:S^*]$$

$$\frac{\mathrm{d}[X^*:P_X]}{\mathrm{d}t} = a_X^*[X^*][P_X] - (d_X^* + k_X^*)[X^*:P_X]$$

$$[Y]_{tot} = [Y] + [Y^*] + [Y:X^*] + [Y^*:P_Y] + [Z:Y^*]$$

$$[P_Y]_{tot} = [P_Y] + [Y^*:P_Y]$$

$$\frac{\mathrm{d}[Y^*]}{\mathrm{d}t} = -a_Y^*[Y^*][P_Y] + d_Y^*[Y^*:P_Y] + k_Y[Y:X^*] - a_Z[Z][Y^*] + (d_Z + k_Z)[Z:Y^*]$$

$$\frac{\mathrm{d}[Y:X^*]}{\mathrm{d}t} = a_Y[Y][X^*] - (d_Y + k_Y)[Y:X^*]$$

$$\frac{\mathrm{d}[Y^*:P_Y]}{\mathrm{d}t} = a_Y^*[Y^*][P_Y] - (d_Y^* + k_Y^*)[Y^*:P_Y]$$

$$[Z]_{tot} = [Z] + [Z^*] + [Z:Y^*] + [Z^*:P_Z]$$

$$[P_Z]_{tot} = [P_Z] + [Z^*:P_Z]$$

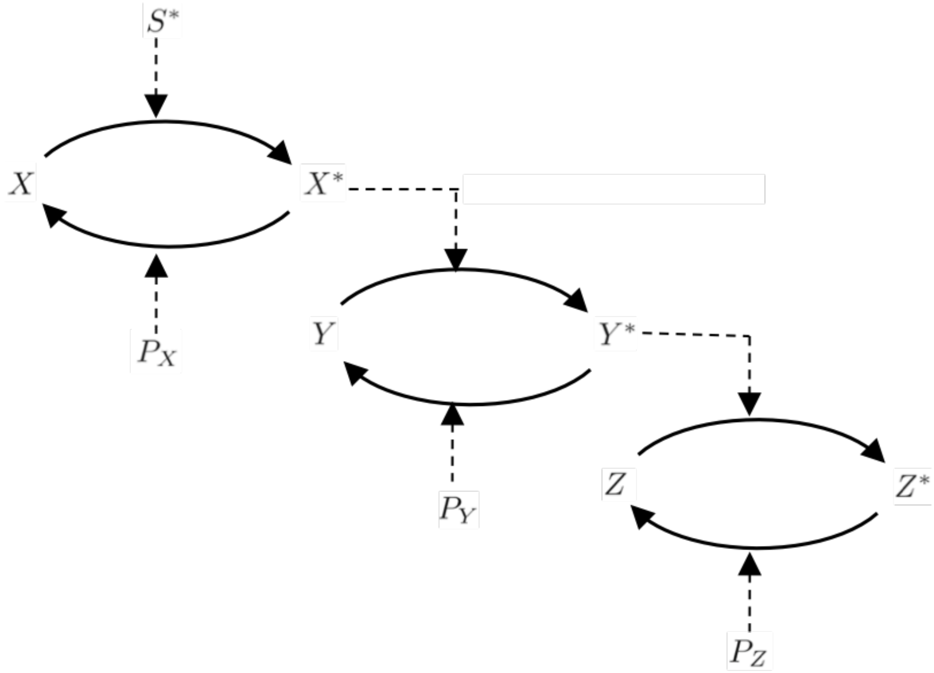
$$\frac{\mathrm{d}[Z^*]}{\mathrm{d}t} = -a_Z^*[Z^*][P_Z] + d_Z^*[Z^*:P_Z] + k_Z[Z:Y^*]$$

$$\frac{\mathrm{d}[Z:Y^*]}{\mathrm{d}t} = a_Z[Z][Y^*] - (d_Z + k_Z)[Z:Y^*]$$

$$\frac{\mathrm{d}[Z^*:P_Z]}{\mathrm{d}t} = a_Z^*[Z^*][P_Z] - (d_Z^* + k_Z^*)[Z^*:P_Z]$$

- Kinetic parameters: $\tilde{a}_X, \tilde{a}_X^*, \tilde{d}_X, \tilde{d}_X^*, \tilde{k}_X, \tilde{a}_Y, \tilde{a}_Y^*, \tilde{d}_Y, \tilde{d}_Y^*, \tilde{k}_Y, \tilde{k}_Y^*, \tilde{a}_Z, \tilde{a}_Z^*, \tilde{d}_Z, \tilde{d}_Z^*, \tilde{k}_Z, \tilde{k}_Z^*$

Key System Parameters



- Concentration ratios

$$\rho^{S/X}, \rho^{P_X/X}, \rho^{X/Y}, \rho^{P_Y/Y}, \rho^{Y/Z}, \rho^{P_Z/Z}$$

- Saturation parameters

$$\tilde{K}_X = \frac{\tilde{d}_X + \tilde{k}_X}{\tilde{a}_X} \qquad \tilde{K}_X^* = \frac{\tilde{d}_X^* + 1}{\tilde{a}_X^*}$$

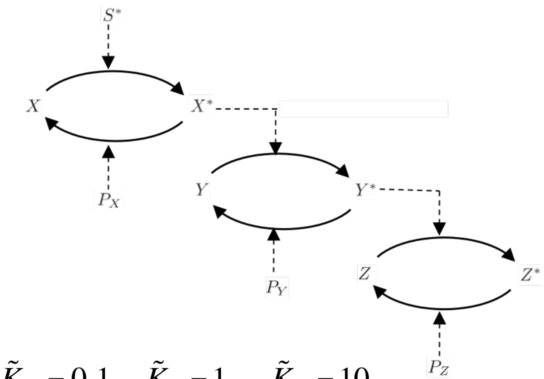
$$\tilde{K}_Y = \frac{\tilde{d}_Y + \tilde{k}_Y}{\tilde{a}_Y} \qquad \tilde{K}_Y^* = \frac{\tilde{d}_Y^* + \tilde{k}_Y^*}{\tilde{a}_Y^*}$$

$$\tilde{K}_Z = \frac{\tilde{d}_Z + \tilde{k}_Z}{\tilde{a}_Z} \qquad \tilde{K}_Z^* = \frac{\tilde{d}_Z^* + \tilde{k}_Z^*}{\tilde{a}_Z^*}$$

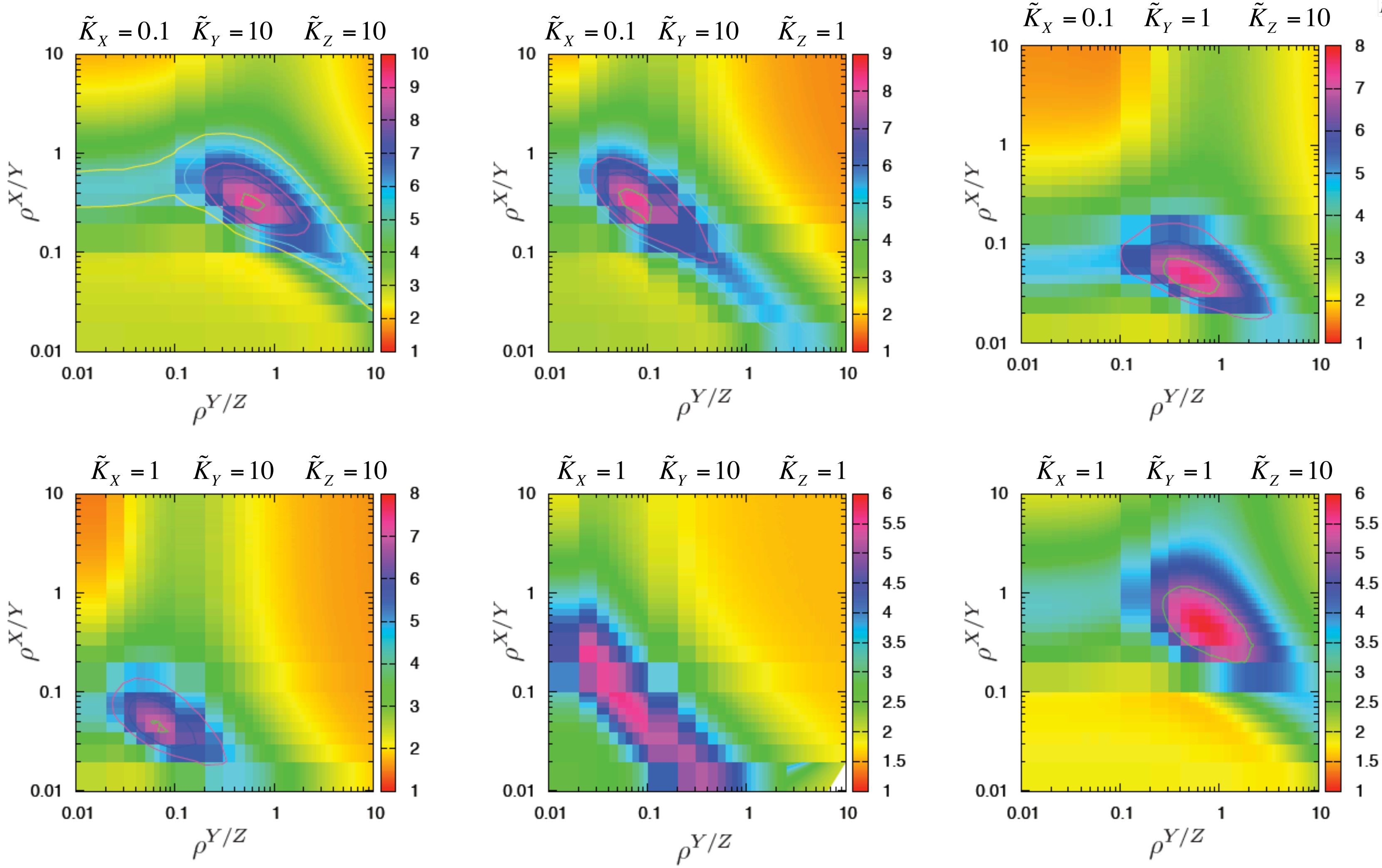
- Activity coefficients

$$\alpha_X = \tilde{k}_X \frac{\rho^{S/X}}{\rho^{P_X/X}} \qquad \alpha_Y = \frac{\tilde{k}_Y}{\tilde{k}_Y^*} \frac{\rho^{X/Y}}{\rho^{P_Y/Y}} \qquad \alpha_Z = \frac{\tilde{k}_Z}{\tilde{k}_Z^*} \frac{\rho^{Y/Z}}{\rho^{P_Z/Z}}$$

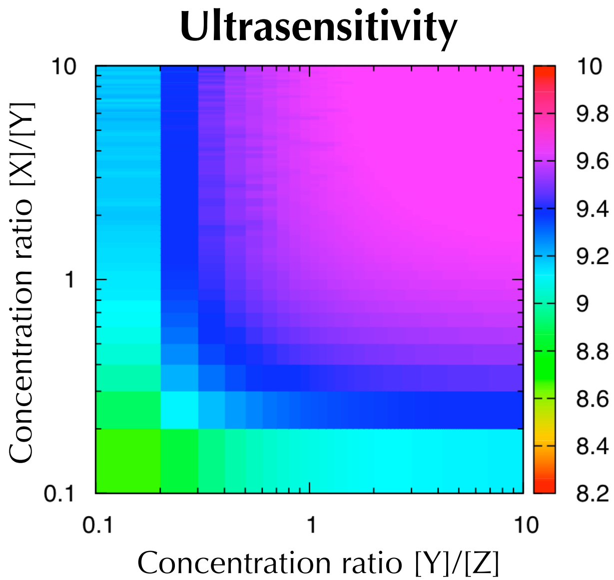
Results: Tricyclic Cascade

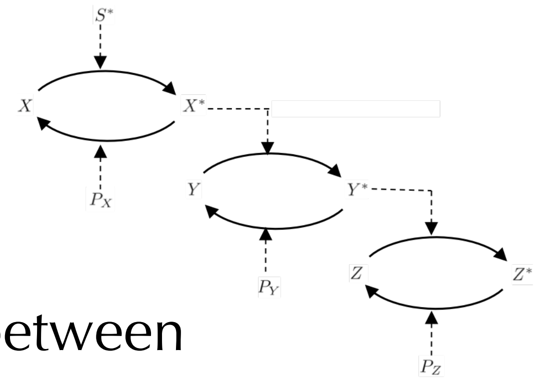


Optimal ultrasensitivity for various combinations of saturation parameters:



Results: Tricyclic Cascade



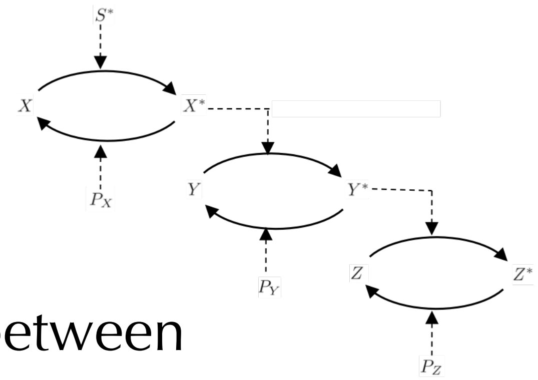


- Optimal ultrasensitivity
for fixed values of ratios between total concentrations of enzymes and substrate

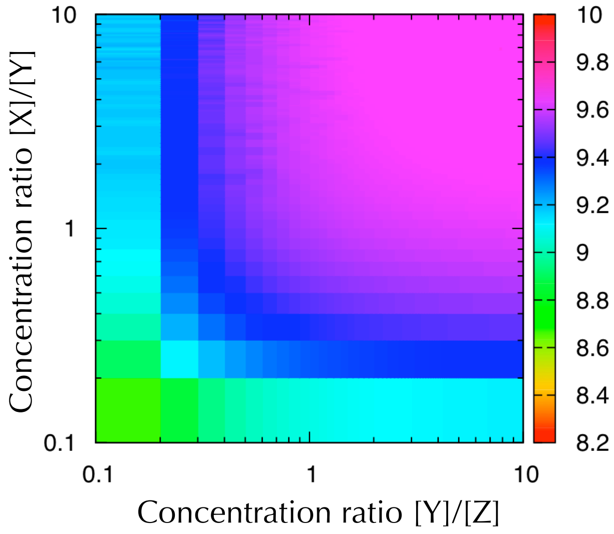
$\rho^{S/X} = 0.1$ $\rho^{P_X/X} = \rho^{P_Y/Y} = \rho^{P_Z/Z} = 0.01$

$\tilde{K}_X^* = \tilde{K}_Y^* = \tilde{K}_Z^* = 0.1$

Results: Tricyclic Cascade



Ultrasensitivity

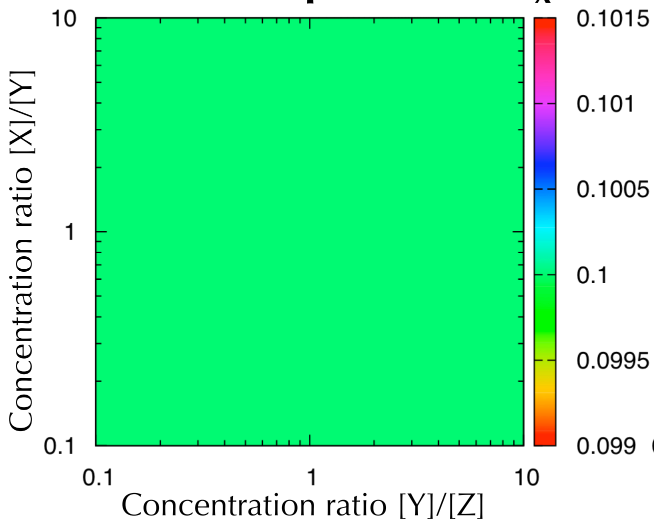


- Optimal ultrasensitivity for fixed values of ratios between total concentrations of enzymes and substrate

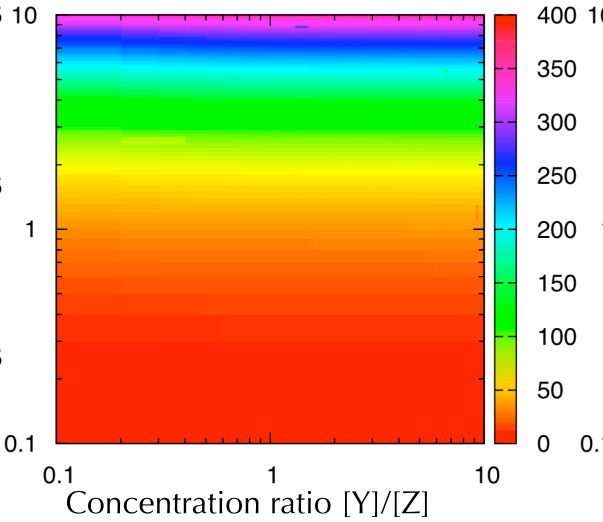
$\rho^{S/X} = 0.1 \qquad \rho^{P_X/X} = \rho^{P_Y/Y} = \rho^{P_Z/Z} = 0.01$

$\tilde{K}_X^* = \tilde{K}_Y^* = \tilde{K}_Z^* = 0.1$

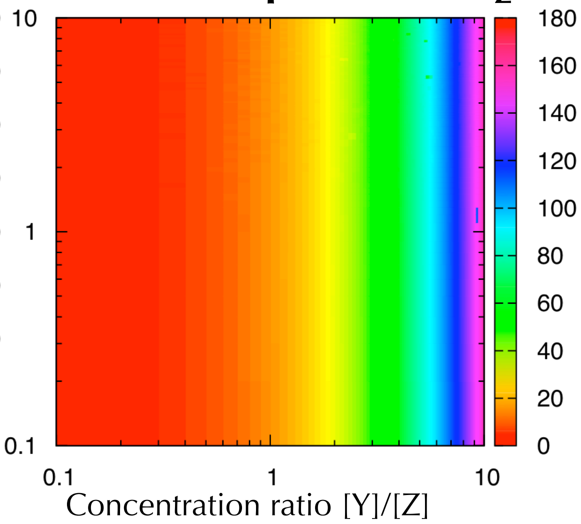
Saturation parameter K_X



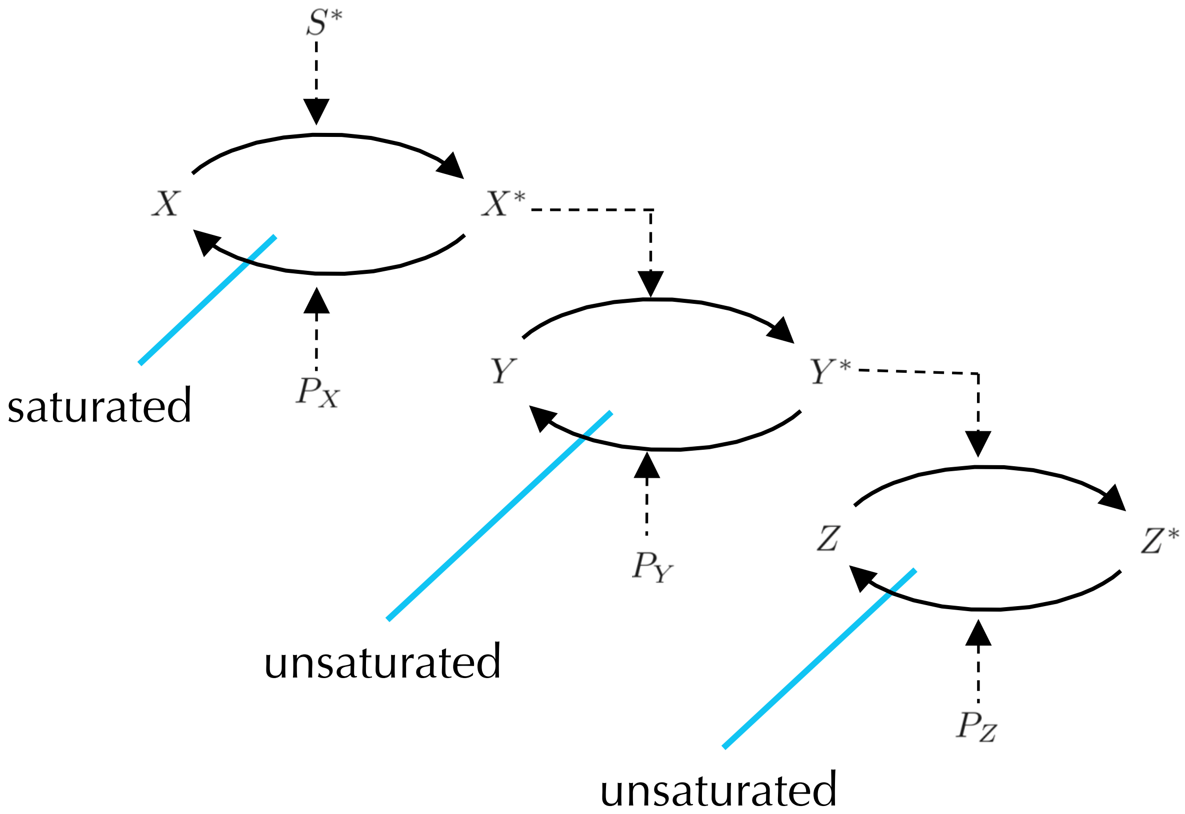
Saturation parameter K_Y



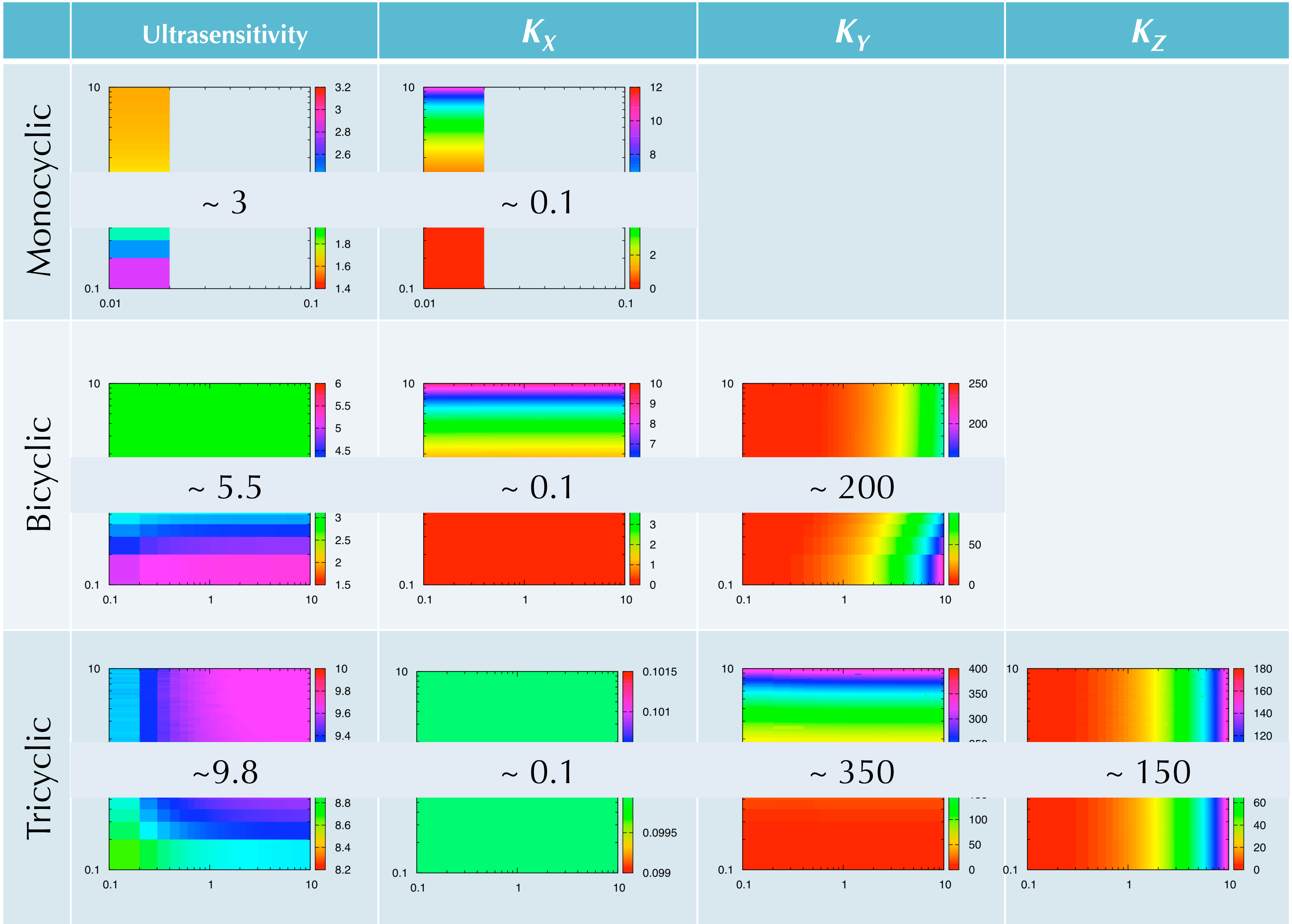
Saturation parameter K_Z



Results: Tricyclic Cascade



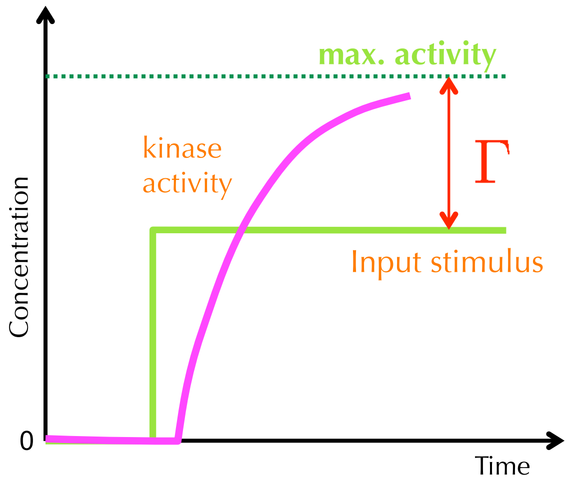
✓Optimal ultrasensitivity is achieved if the first kinase is saturated by its target kinase, but not the subsequent two kinases.



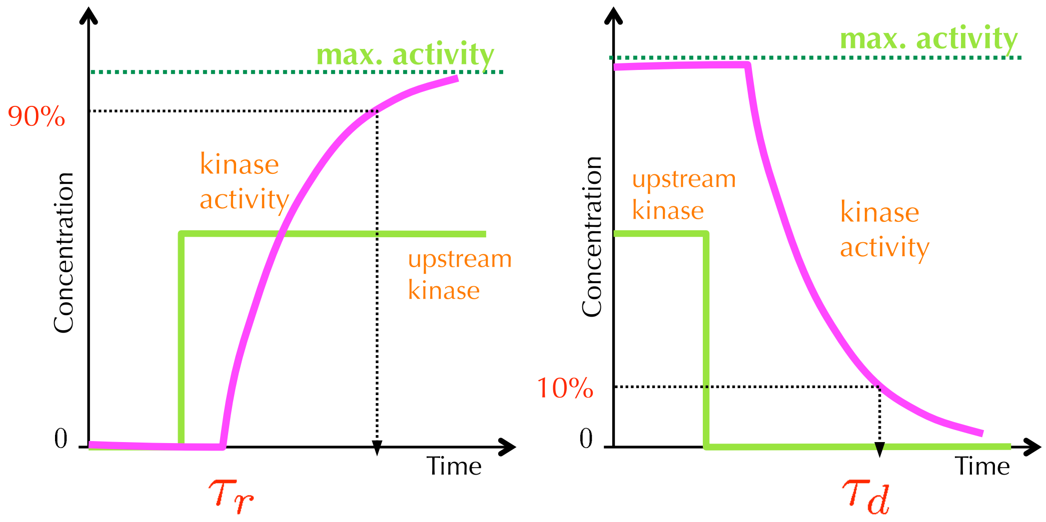
Ultrasensitivity
K_X
K_Y
K_Z
Monocyclic
~ 3
~ 0.1
Bicyclic
~ 5.5
~ 0.1
~ 200
Tricyclic
~9.8
~ 0.1
~ 350
~ 150

Design Objectives

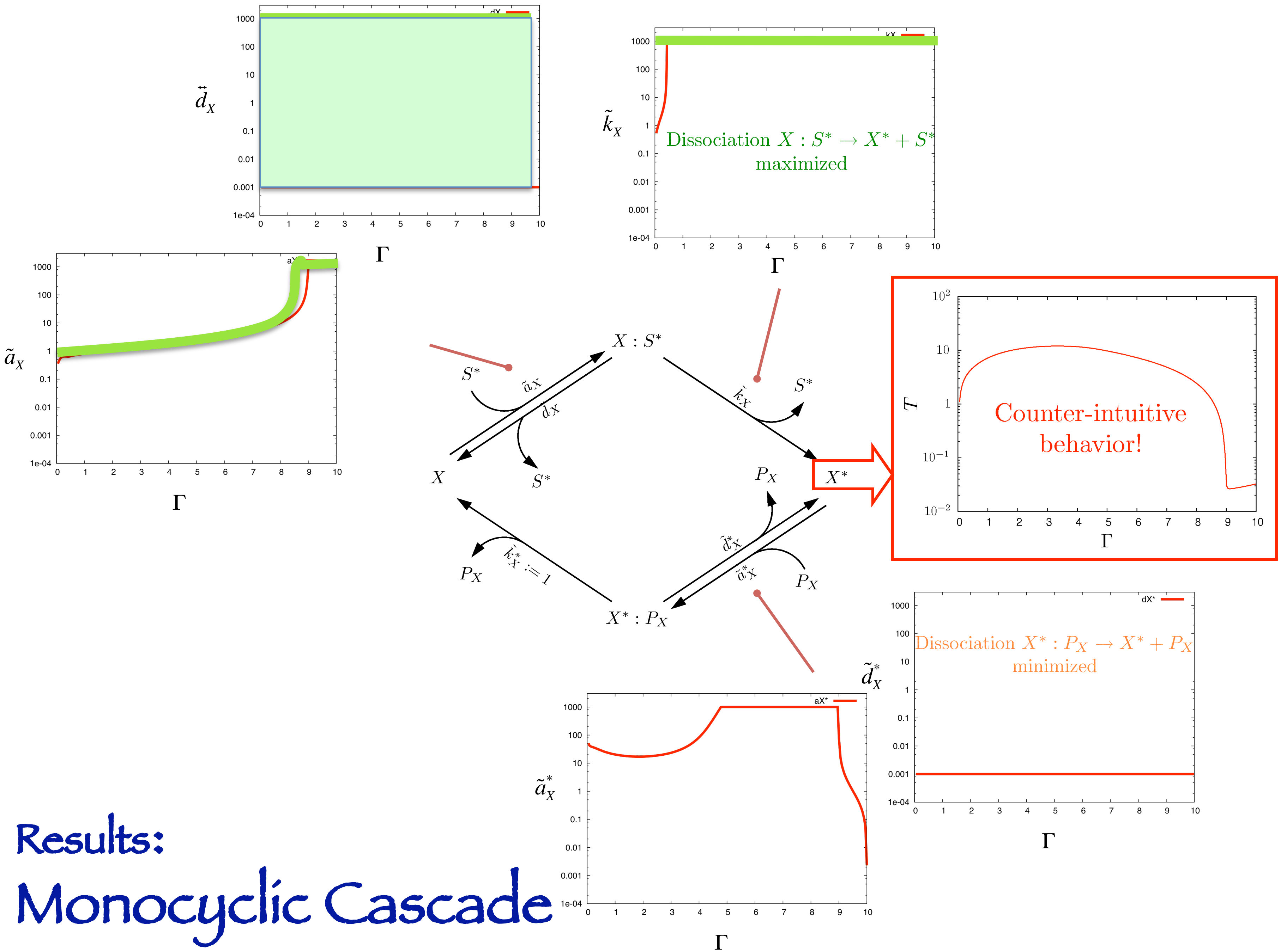
Amplification:



Signal Propagation Time: $T \approx \tau_r + \tau_d$



- **Amplification** in signaling cycles - a measure of response strength
- $\mathbf{T_r}$ - measure of how fast a signal is transduced through a cycle and time needed to reach 90% of the maximum substrate activation
- $\boldsymbol{\tau_d}$ – time needed for the substrate activity to decrease to within 10% of the ground state



Results:

Monocyclic Cascade

Summary

- ✓ Optimal multicycle cascades may not correspond to multiple levels of an optimal single level cascade

- ✓ The larger the number of levels in the cascade, the more robust that cascade

  - variation in concentration regimes

- ✓ Fast signal propagation can be achieved with different sets of kinetic parameters

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