Cell Systems

Math | Bio

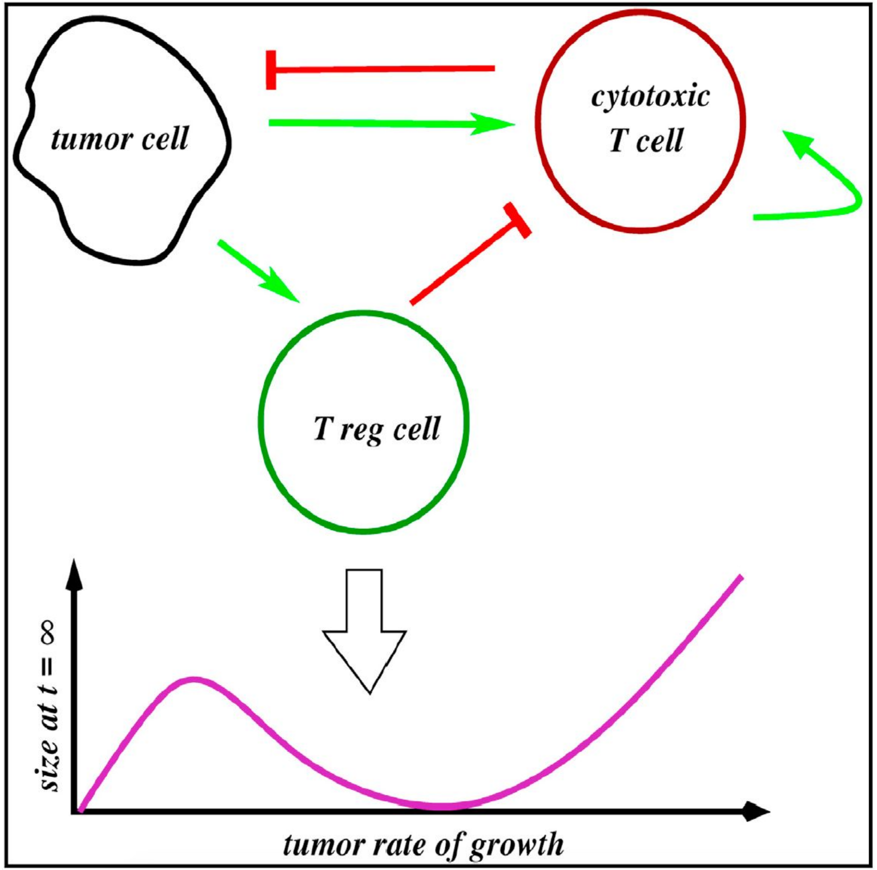
A Dynamic Model of Immune Responses to Antigen Presentation Predicts Different Regions of Tumor or Pathogen Elimination

Eduardo Sontag

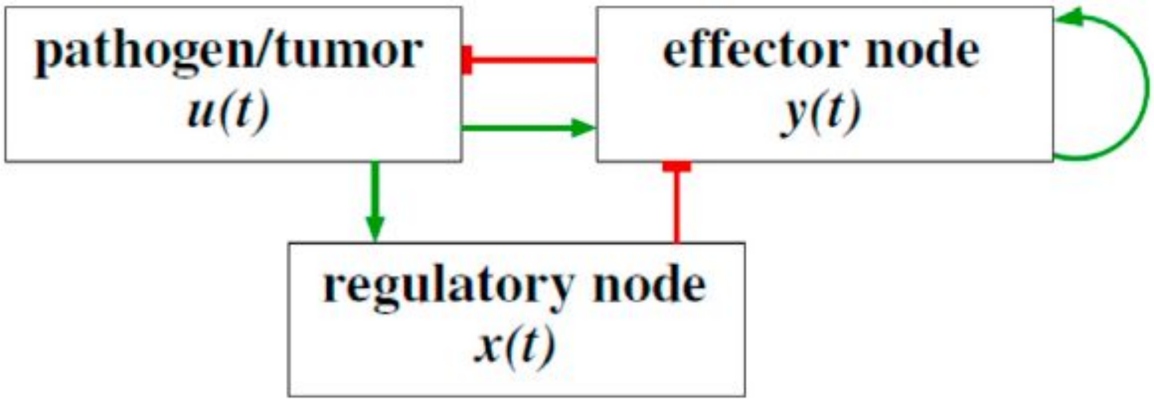
a presentation by
Friedrich Puttkammer & Lasse Bonn

Introduction

- Simple model
  → 4 **response zones**
  → **experimental** findings



Our System



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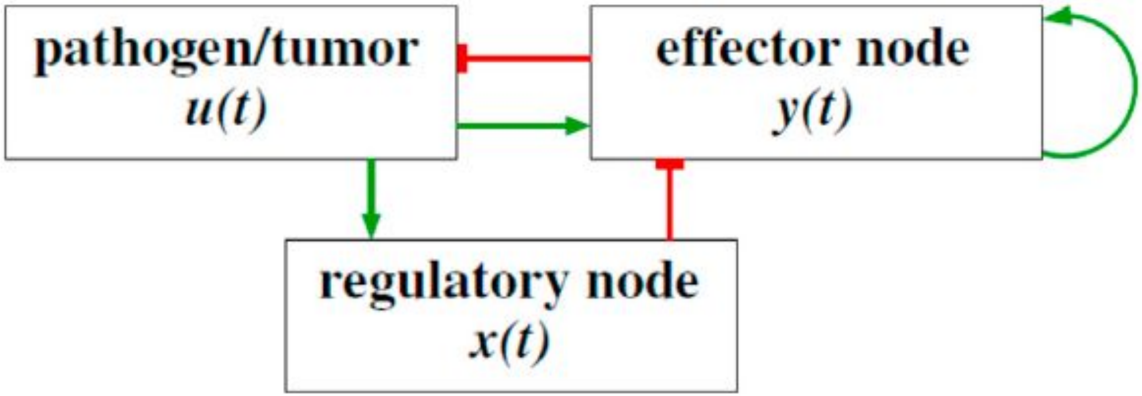
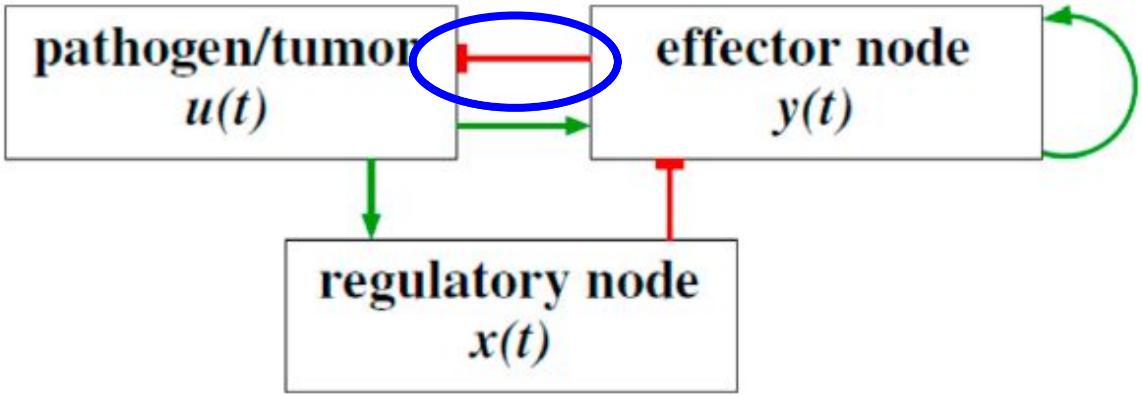


$$\dot{u} = (\boxed{\lambda} - \kappa y)u$$
$$\dot{x} = -\delta_x x + \beta u$$
$$\dot{y} = h(u/x) + f(y)$$

Our System



$$\dot{u} = (\lambda \boxed{- \kappa y})u$$

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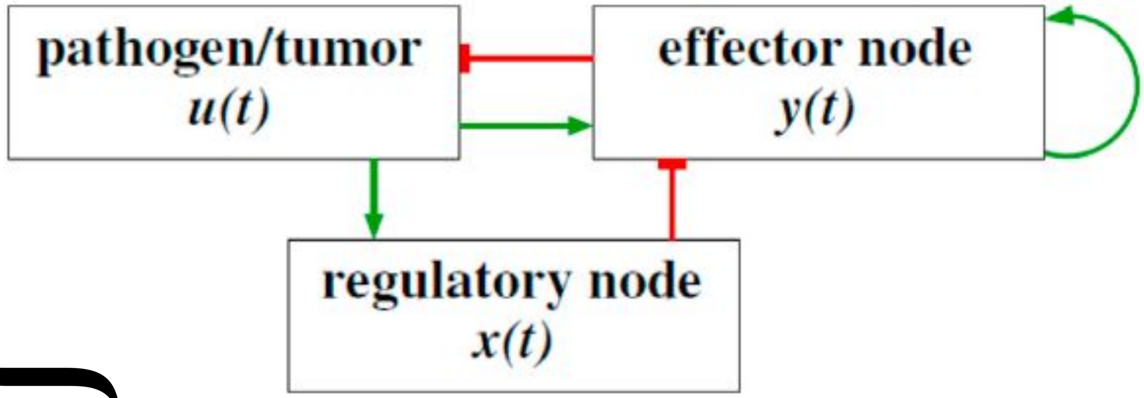

$$\dot{u} = (\overbrace{\boxed{\lambda - \kappa y}}^{v})u$$
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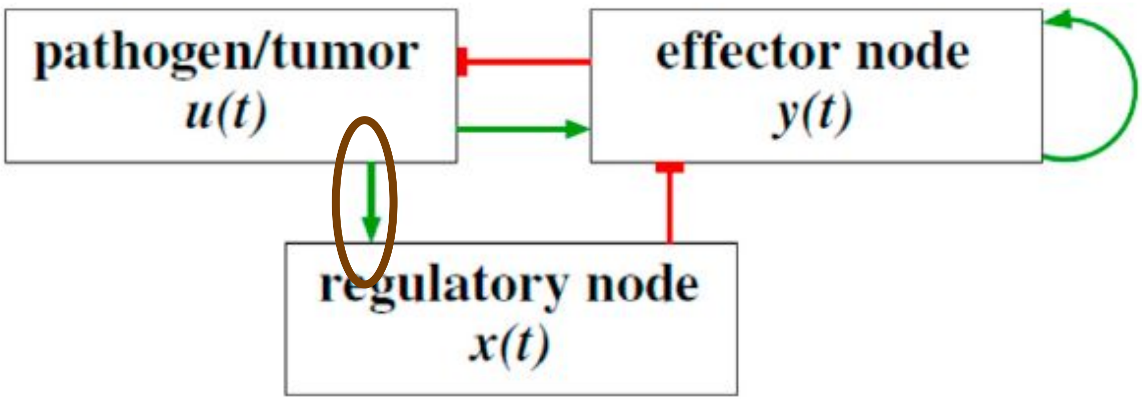
Our System



$$\dot{u} = (\lambda - \kappa y)u$$

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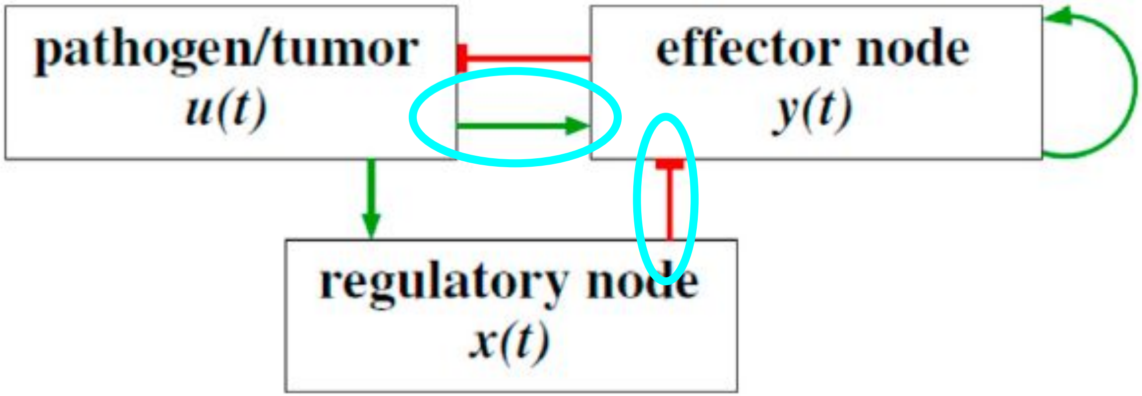
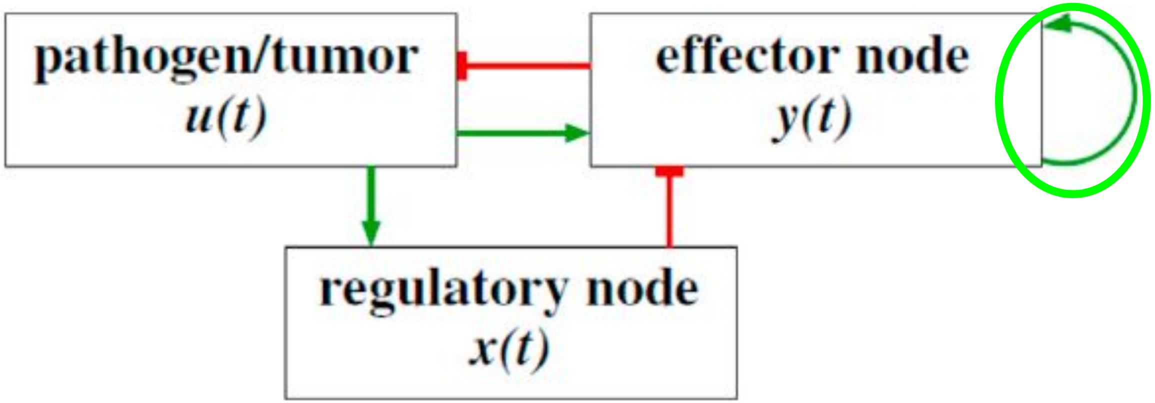


$$\dot{u} = (\lambda - \kappa y)u$$

$$\dot{x} = -\delta_x x + \beta u$$

$$\dot{y} = \boxed{h(u/x)} + f(y)$$

Our System



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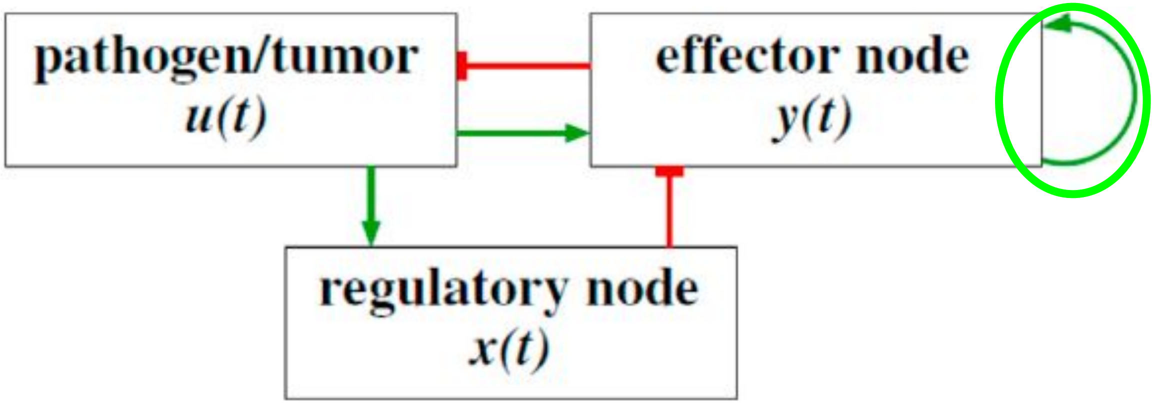

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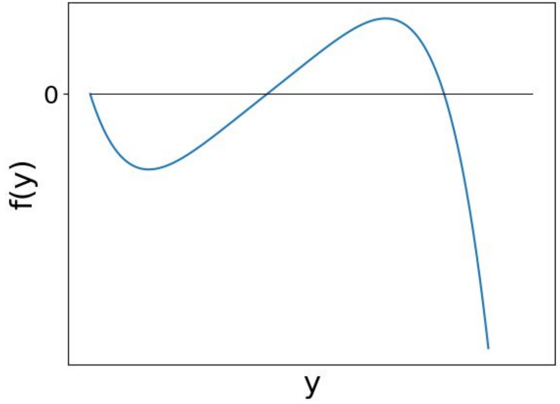
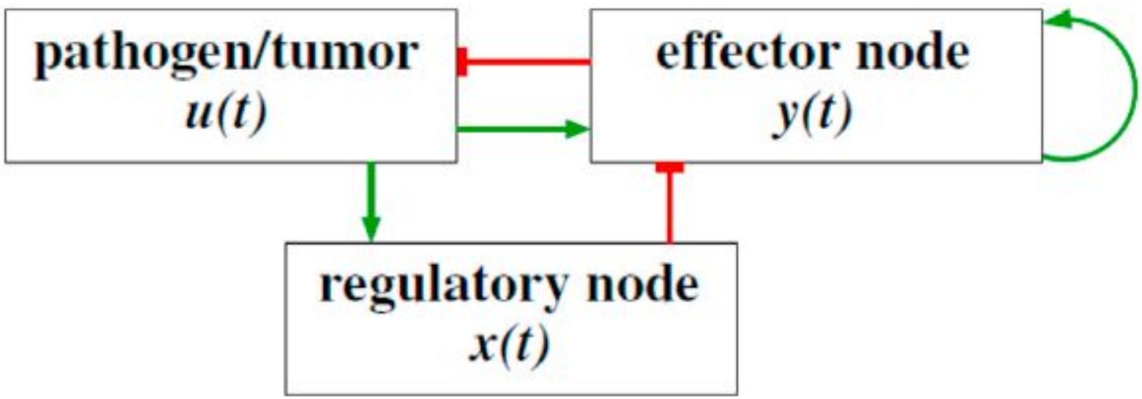


Our System



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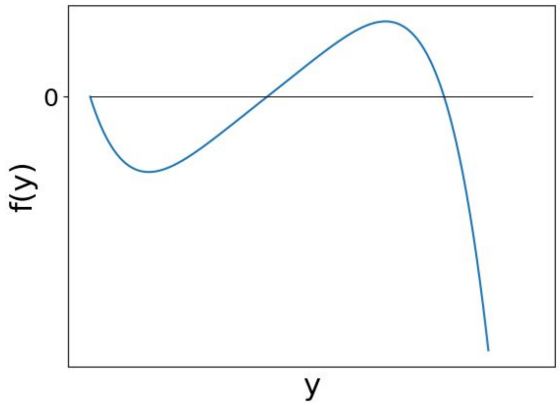
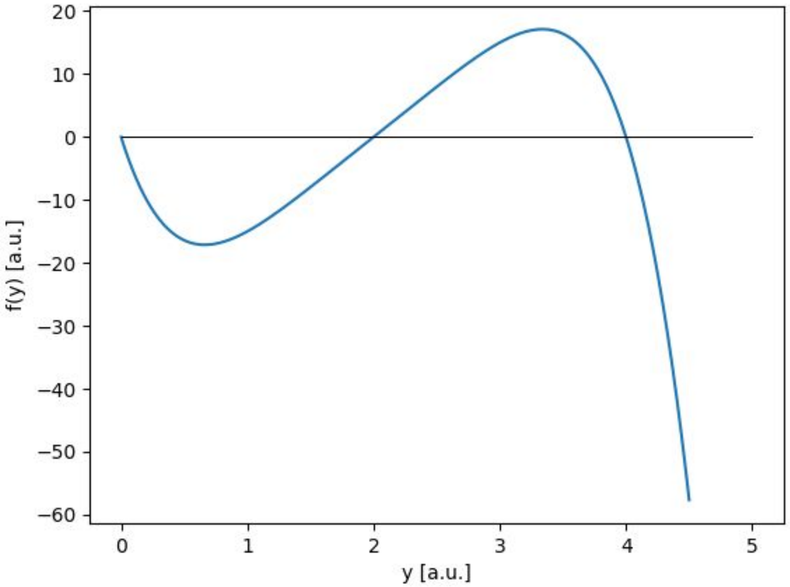


Self dependence of y



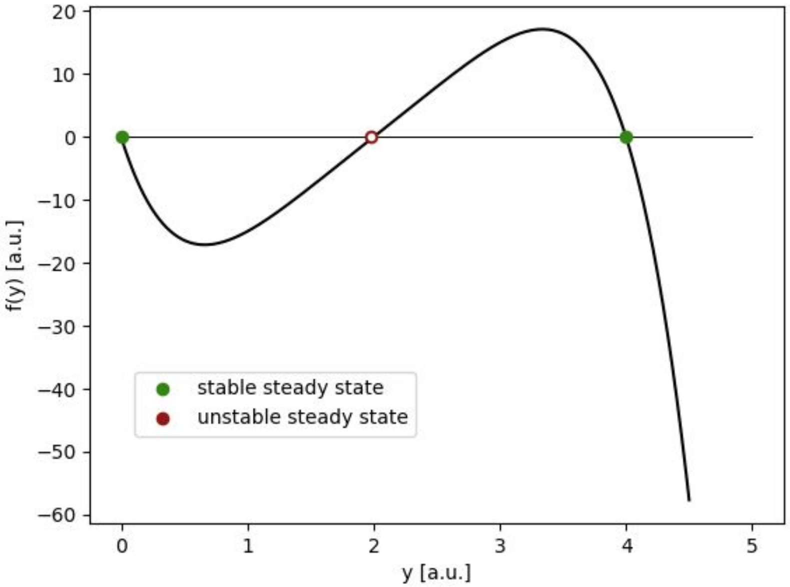
Increase:

- **autocatalytic** feedback

Decrease:

- **degradation** / deactivation
- **homeostasis** (e.g. through apoptosis)

Bistability



- Low y values:

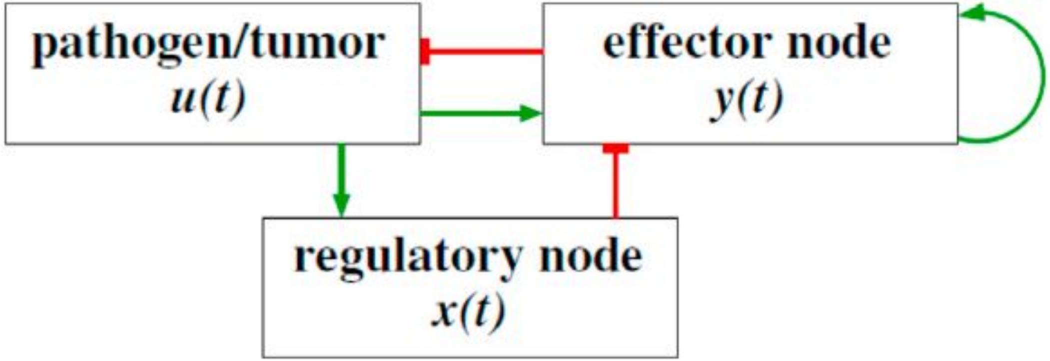
  → **information discarded**

- High y values:

  → **“memory”**

- Simplified system

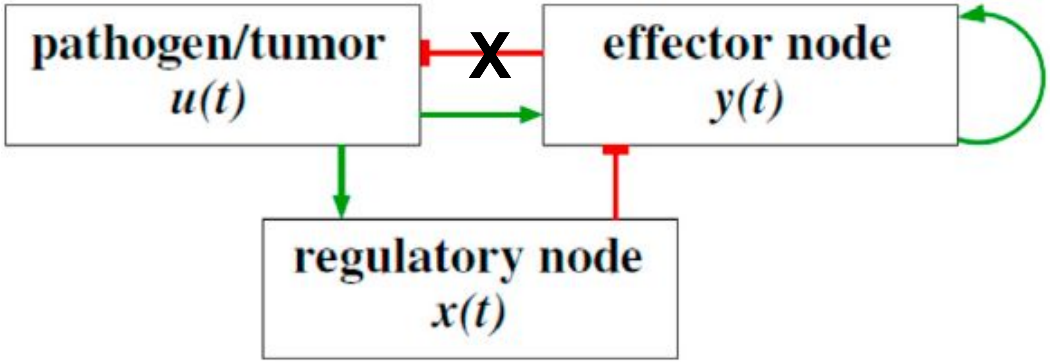
  → mathematical analysis

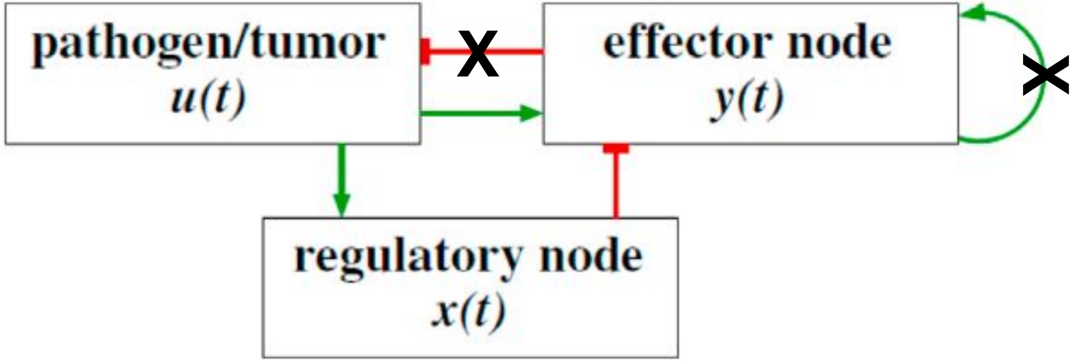


- Simplified system

  → mathematical analysis

- **u** = external signal





- Simplified system

  → mathematical analysis

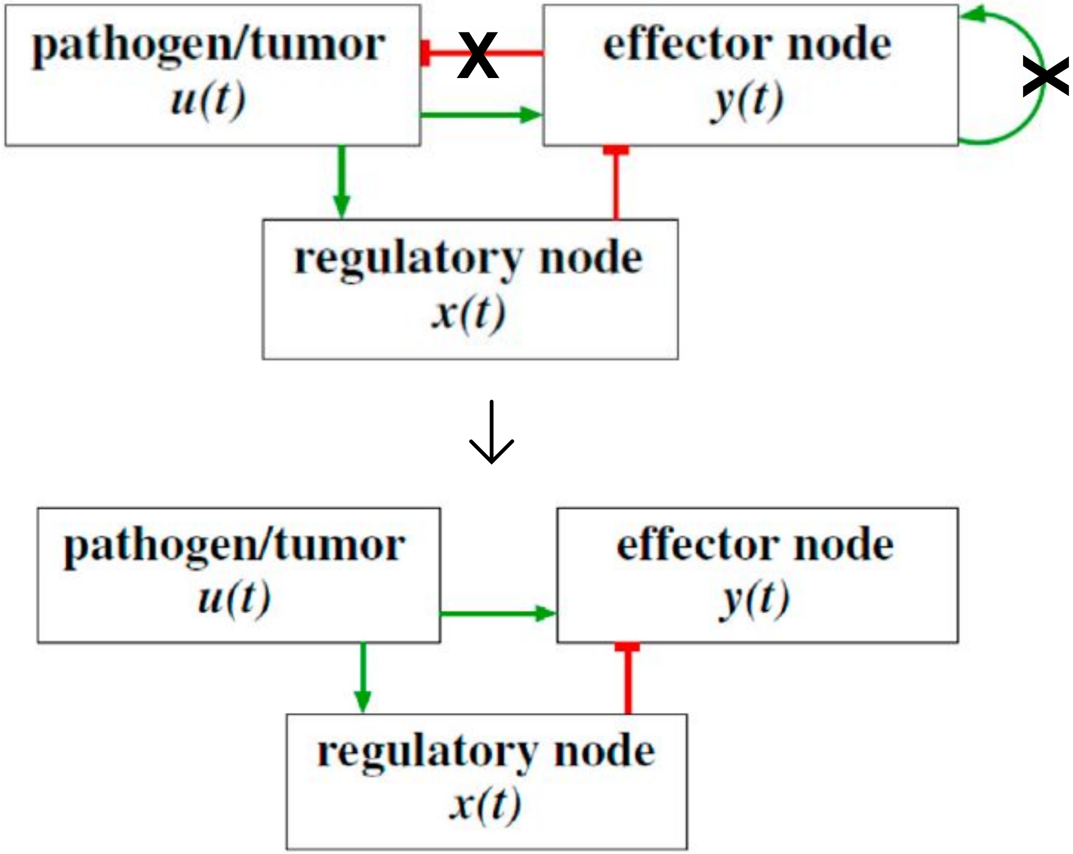
- **u** = external signal
- No autocatalytic feedback

Incoherent feedforward loop

- Simplified system

  → mathematical analysis

- **u** = external signal
- No autocatalytic feedback



Incoherent feedforward loop

1. **u** = external signal

$$\dot{u} = (\lambda - \kappa y)u$$
$$\dot{x} = -\delta_x x + \beta u$$
$$\dot{y} = h(u/x) + f(y)$$

Incoherent feedforward loop

1. **u** = external signal
2. No autocatalytic feedback

→ no homeostatic terms necessary

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Incoherent feedforward loop

1. **u** = external signal
2. No autocatalytic feedback

    → no homeostatic terms necessary

3. **h** as linear function

$$\dot{x} = -\delta_x x + \beta u$$
$$\dot{y} = h(u/x) - \delta_y y$$

Incoherent feedforward loop

1. **u** = external signal
2. No autocatalytic feedback

   → no homeostatic terms necessary

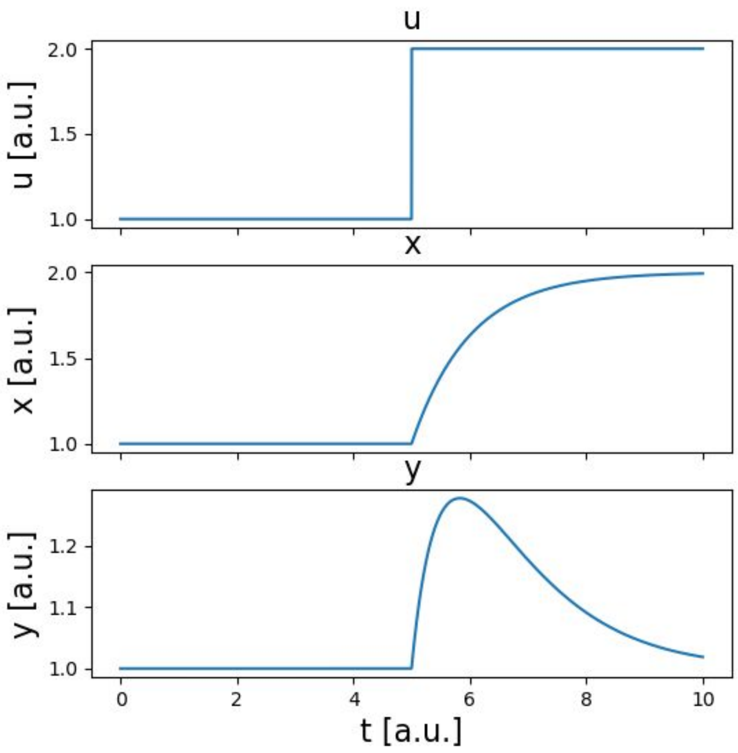
3. **h** as a linear function

$$\dot{x} = -\delta_x x + \beta u$$
$$\dot{y} = \mu u / x - \delta_y y$$

Properties

- Contradicting (incoherent) pathways

  → **short** activity **burst**



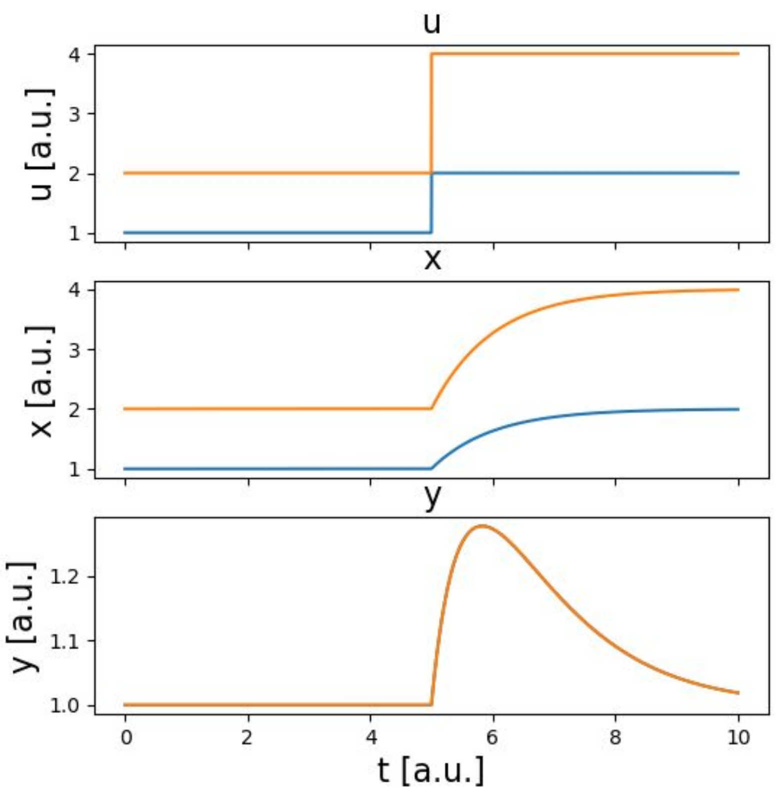
Reaction to a **step function**

Properties

- Contradicting (incoherent) pathways

  → **short** activity **burst**

- **Scale invariance**



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$$\dot{y} = \mu \frac{\epsilon u}{\epsilon x} - \delta_y y$$

$$\Leftrightarrow$$

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Properties

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Properties

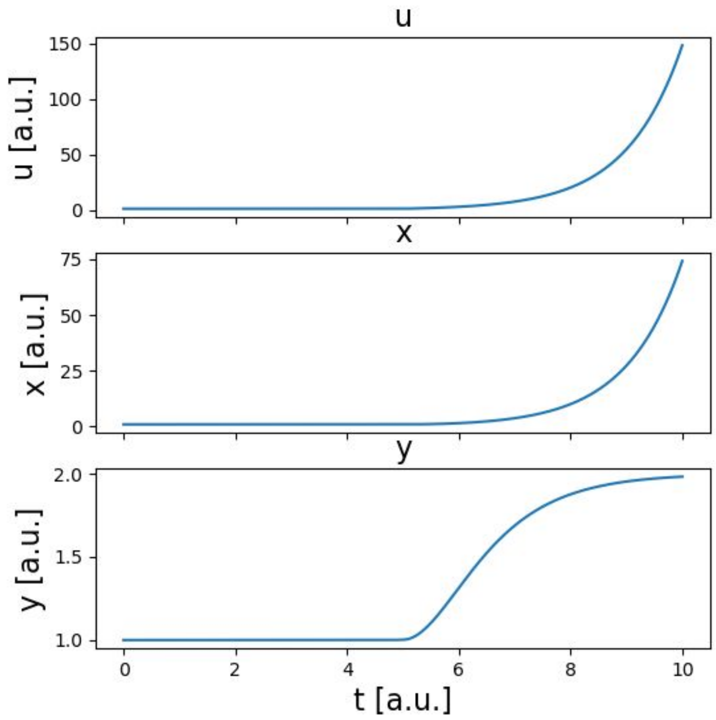
- Contradicting (incoherent) pathways

  → **short** activity **burst**

- **Scale invariance**

- exponential growth

  → **constant reply**
  (proportional to growth rate)



Reaction to an **exponential** signal

Going back to the more complex system...

$$
\begin{aligned}
\dot{u} &= (\lambda - \kappa y)u \\
\dot{x} &= -\delta_x x + \beta u \\
\dot{y} &= h(u/x) + f(y)
\end{aligned}
$$

Transformation with $p = u/x$

$$\dot{u} = (\lambda - \kappa y)u$$

$$\dot{p} = p(\delta_x + \lambda - \kappa y - \beta p)$$
$$\dot{y} = h(p) + f(y)$$

- **u** decoupled from **p** and **y**

→ **2 dimensional** analysis possible

Nullclines

$$\boxed{\text{Note: } y, p \geq 0}$$

$$\dot{y} = h(p) + \boxed{f}(y)$$

Nullclines

$$\dot{y} = h(p) + f(y)$$

$$N_y : p = h^{-1}(\boxed{-f}(y))$$

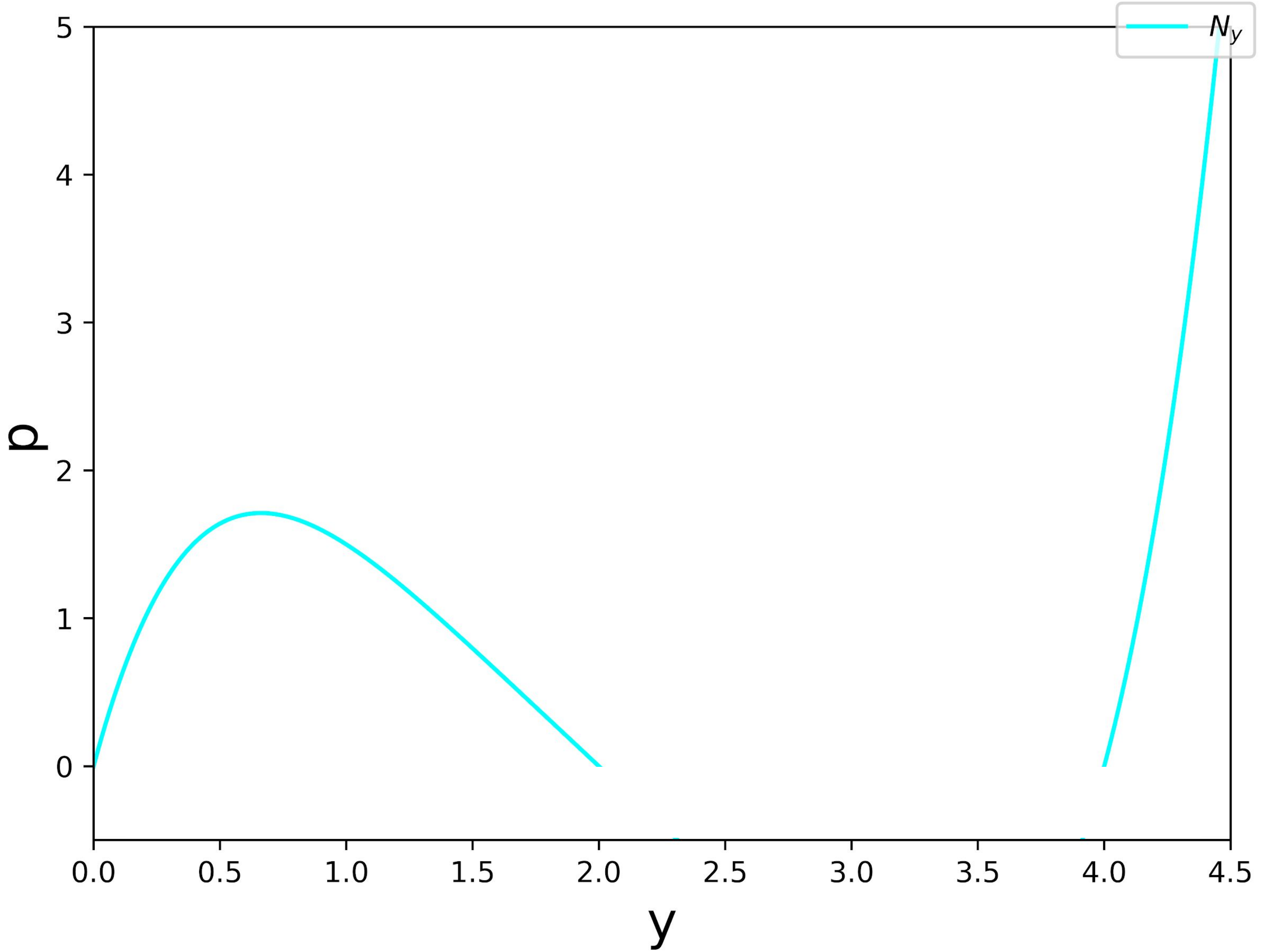
Nullclines

$$\dot{y} = h(p) + f(y)$$

$$N_y : p = h^{-1}(-f(y))$$

for $h(p) = \mu p$

$$\rightarrow p = \boxed{-f}(y)/\mu$$



N_y
p
y
0
1
2
3
4
5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5

Nullclines

$$N_1 : p = h^{-1}(-f(y))$$

$$\rightarrow p = -f(y)/\mu$$

$$\boxed{\text{Note: } y, p \geq 0}$$

$$N_{2a} : p = 0$$

$$N_{2b} : p = (1/\beta)(\delta_x + \lambda - \kappa y)$$

Nullclines

$$N_1 : p = h^{-1}(-f(y))$$

$$\rightarrow p = -f(y)/\mu$$

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$$N_{2a} : p = 0$$

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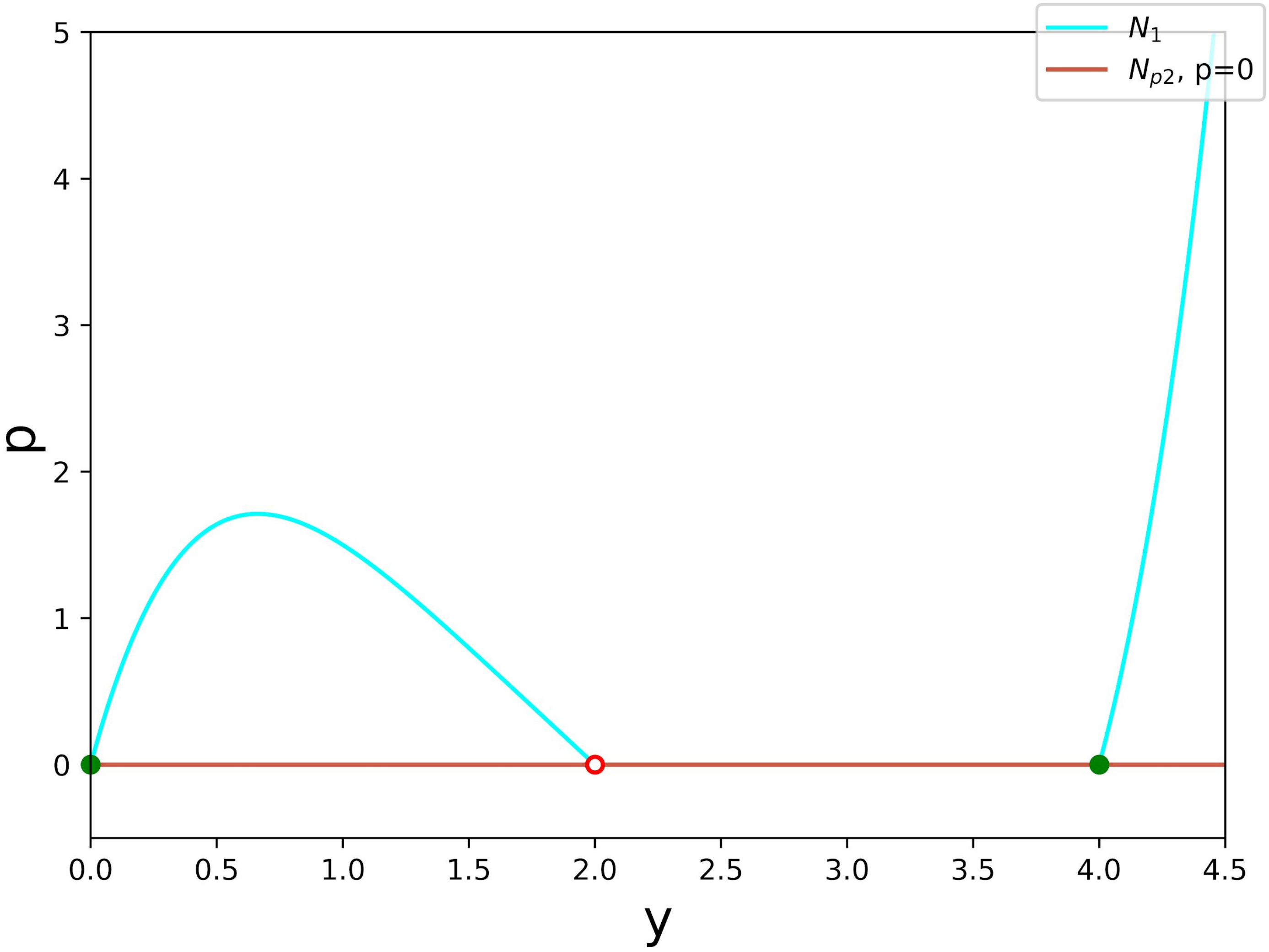
Nullclines

$$\dot{p} = p(\delta_x + \lambda - \kappa y - \beta p)$$

$$N_{p1} = 0$$



N_1
N_{p2}, p=0
p
y
0
1
2
3
4
5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5

Nullclines

$$\dot{p} = 0 = \bar{p}(\delta_x + \lambda - \kappa y - \beta\bar{p})$$

$$0 = (\delta_x + \lambda - \kappa y - \beta\bar{p})$$

Nullclines

$$0 = (\delta_x + \lambda - \kappa y - \beta \bar{p})$$

$$N_{p2} : \bar{p} = (1/\beta)(\delta_x + \lambda - \kappa y)$$

Nullclines

$$0 = (\delta_x + \lambda - \kappa y - \beta \bar{p})$$

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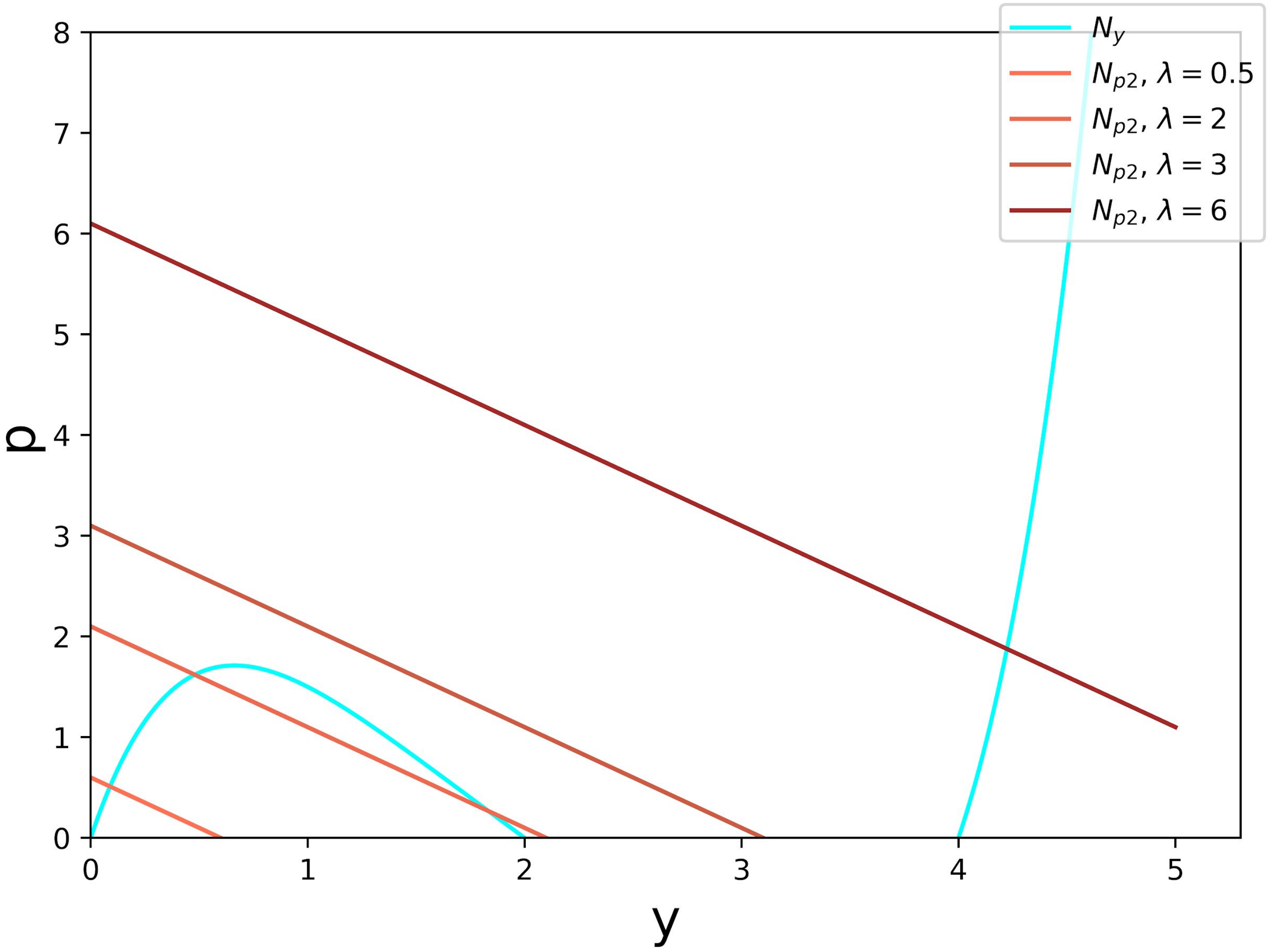
N_y
N_{p2}, $\lambda = 0.5$
N_{p2}, $\lambda = 2$
N_{p2}, $\lambda = 3$
N_{p2}, $\lambda = 6$
p
y
0
1
2
3
4
5
6
7
8

reminder: $\dot{u} = (\boxed{\lambda - \kappa y})u = vu$

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$$0 = (\delta_x + \boxed{\lambda - \kappa y} - \beta\bar{p}) \qquad (N_{p2})$$

reminder: $\dot{u} = (\boxed{\lambda - \kappa y})u = vu$

$$0 = (\delta_x + \boxed{\lambda - \kappa y} - \beta\bar{p})$$

$$vu = \boxed{\lambda - \kappa y} = \beta\bar{p} - \delta_x$$

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Threshold for death:

$$v = 0 = \bar{p} - \delta_x/\beta$$

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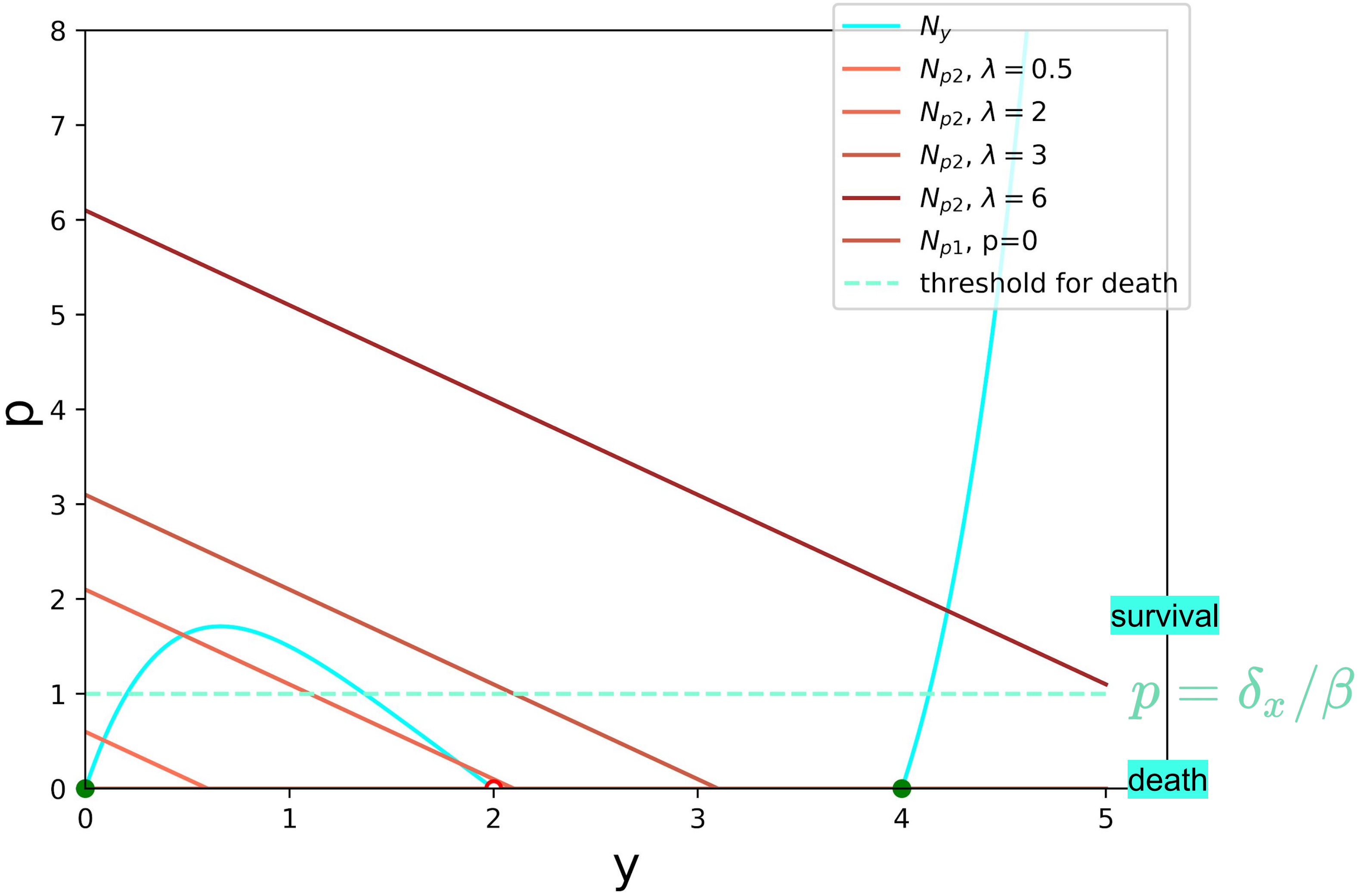
$$v = 0 = \bar{p} - \delta_x / \beta$$

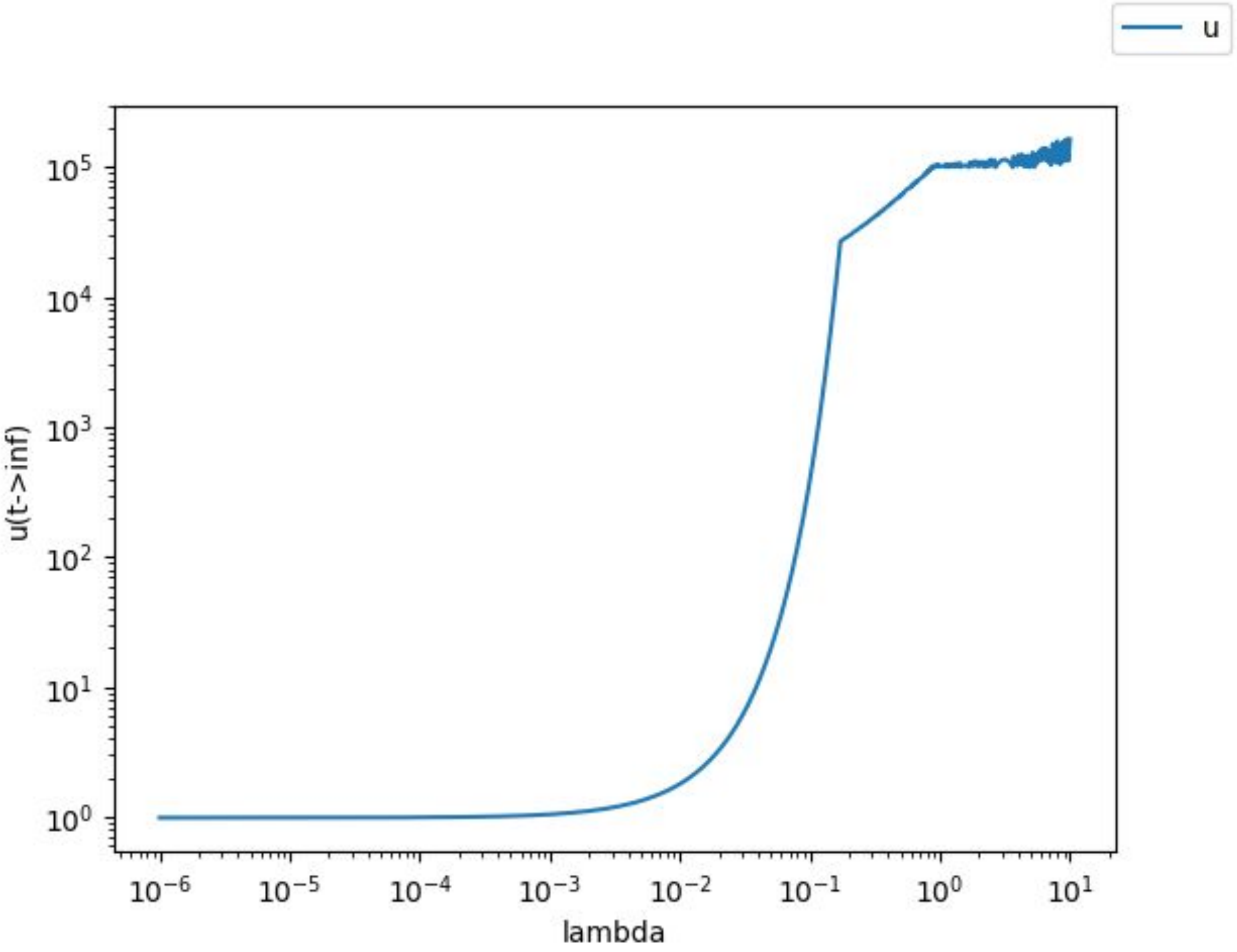
$$\bar{p} < \delta_x / \beta \rightarrow v < 0 : \text{elimination}$$

$$\bar{p} > \delta_x / \beta \rightarrow v > 0 : \text{ growth or tolerance}$$

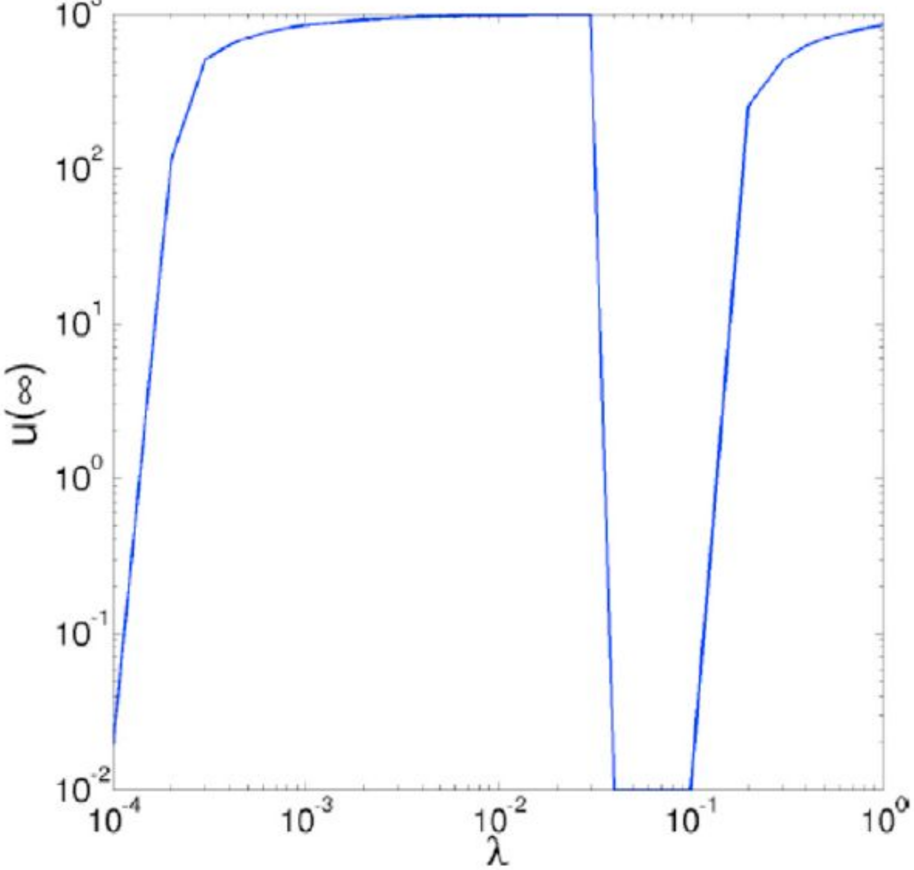


N_y
N_{p2}, $\lambda = 0.5$
N_{p2}, $\lambda = 2$
N_{p2}, $\lambda = 3$
N_{p2}, $\lambda = 6$
N_{p1}, p=0
threshold for death
survival
$p = \delta_x/\beta$
death
p
y
0
1
2
3
4
5
6
7
8

4 phase growth



4 phase growth plot



Acknowledgements

Thanks to Ana for helping us!