Integral feedback control in Erk1/2 signalling

Franziska Witzel
Computational Modelling in Medicine
EGF 

[Sos Grb2] Ras 

Raf 

Mek 

Erk 

RSK 

Erk target 

Elk1 

c-Fos, EGR1
Erk target overexpression!
Erk overexpression

the more Erk, the more active Erk!
Robustness to Erk overexpression

- JUNB
- FOSL1
- FOSL2
- DUSP6
- SPRY4
- SPRY2
- ARRDC4
- ZFP36
- KLF10
- CDKN1A
- EGR1
- EGR2
- EGR3
- DUSP1
- DUSP4
- DUSP5
- IER2
- IER3
- FOS
- FOSB

Time [h]

Log2 fold induction

Nucleus
Robustness to Erk overexpression

- Time after stimulation
- ppErk
- Log2 fold induction

Genes involved:
- EGR1, EGR2, EGR3
- DUSP1, DUSP4, DUSP5
- IER2, IER3
- FOS, FOSB
- JUNB, FOSL1, FOSL2
- DUSP6, SPRY4, SPRY2, ARRDC4, ZFP36, KLF10, CDKN1A
Cruise control

Several unpredictable factors like weight of the car, slope of the street …
Cruise control

Several unpredictable factors like weight of the car, slope of the street …

Actuate throttle → Car → Sense speed

Integral feedback control

$- \int (v_{cur} - v_{set})$

Robustness in mathematical terms:
stable steady state of desired velocity
Control of Erk activity

Growth factor

(de)phosphorylate

(activity of Erk)

Sense activity

compute
Raf as integrating unit

Set value of activity $y_0$

Measured value of activity $y_1$

Time after stimulation $y_1(t)$
treat with EGF

measure phosphorylation of cRaf on Ser289/296/301

measure ppErk

nucleus
Accumulation of negative phospho marks on cRaf

treat with EGF

![Diagram of signal transduction pathway involving Ras, Raf, Mek, and Erk proteins, with a focus on the accumulation of phospho marks over time in both minutes (0-12) and hours (0-6).](image)

- **Intensity (A.U.)** over time [min]:
  - Green line: pErk_total_norm
  - Red line: phospho.cRaf_norm

- **Intensity (A.U.)** over time [h]:
  - Green line: pcRaf_norm
  - Red line: pErk_norm
  - Blue line: pErk_plex

- **Graph annotations**:
  - Treat with EGF
  - Accumulation of negative phospho marks on cRaf
treat with EGF/TMX ...

... inhibit Mek

measure phosphorylation of cRaf on Ser289/296/301

measure ppErk
treat with EGF/TMX ...

... inhibit Mek


intensity [A.U.]

intensity [A.U.]

intensity [A.U.]
treat with EGF/TMX ...

... inhibit Mek

\( t_{1/2} = 1.24h \)

\( t_{1/2} = 0.94h \)
Take home message

- Strong robustness of MAPK signaling to perturbations in expression levels of Erk
- Integral feedback might establish this robustness