lecture 2 5/12/2004

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brief review of lecture 1

* similarity between { human designed control system
  adaptation / homeostasis in biological systems

* human designed syst
  control theory well developed for the design & analysis
  examples of application of control theory to the analysis of biological system scarce

* basic concepts of control theory
  - △ block diagram (satellite attitude control example)
  - △ 3 basic types of feed backs
    P I D controller
  - △ Laplace transform as a tool to analyze feedback control systems
    differential eq → algebraic eq.
    steady state
    stability → location of poles
    transient dynamics

example - modeling internal nutrient homeostasis, example of zinc

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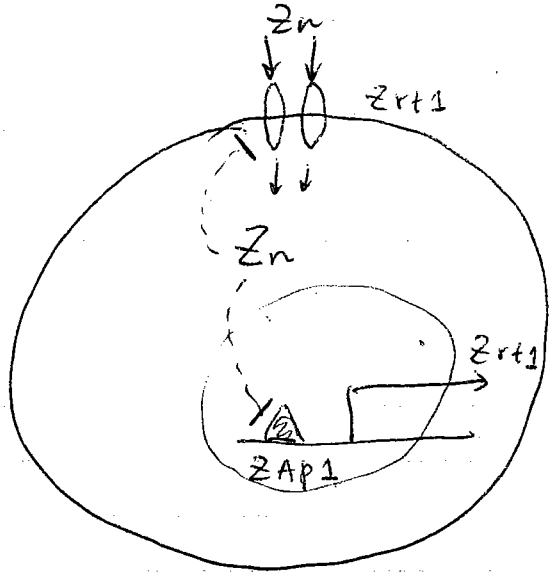
A simplified picture



two different feedbacks

transcriptional: high Zn → shut down transcription of transporter

protein degradation: high Zn → induce endocytosis of transporter → vacuole → degraded

A minimal model:

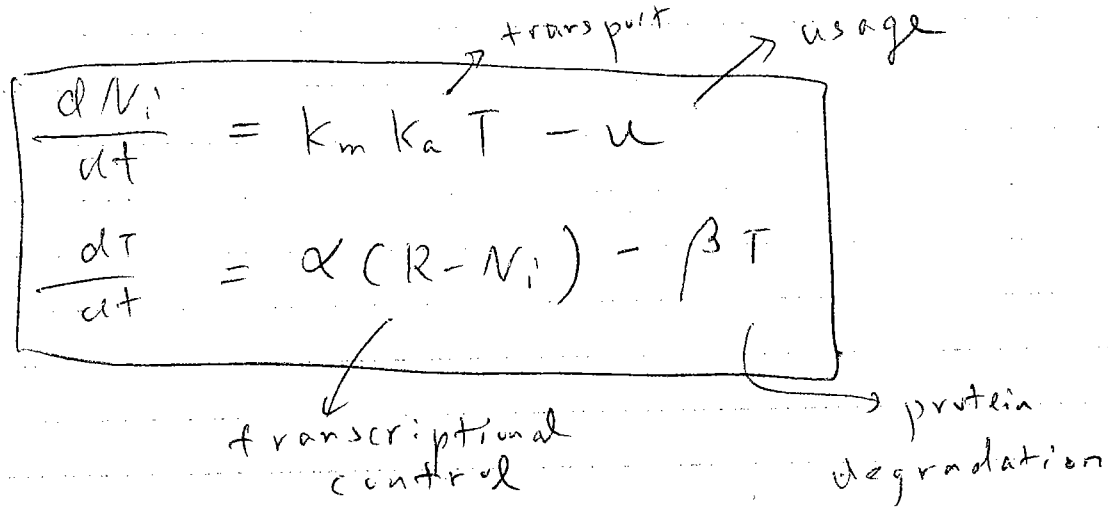
dynamics of

T : transporter

N_i : internal nutrient concentration

with feedbacks both transcriptional post-translational

A simple model proposed by
Erin O'shea & Mike Springer



$k_a = \frac{N_e}{N_e + K_t}$ fraction bound by external nutrient

k_m : maximum transport rate of a single transporter

R : set point

$\beta = \beta_0 k_a$, degradation of nutrient bound transporter

Laplace transform the equations

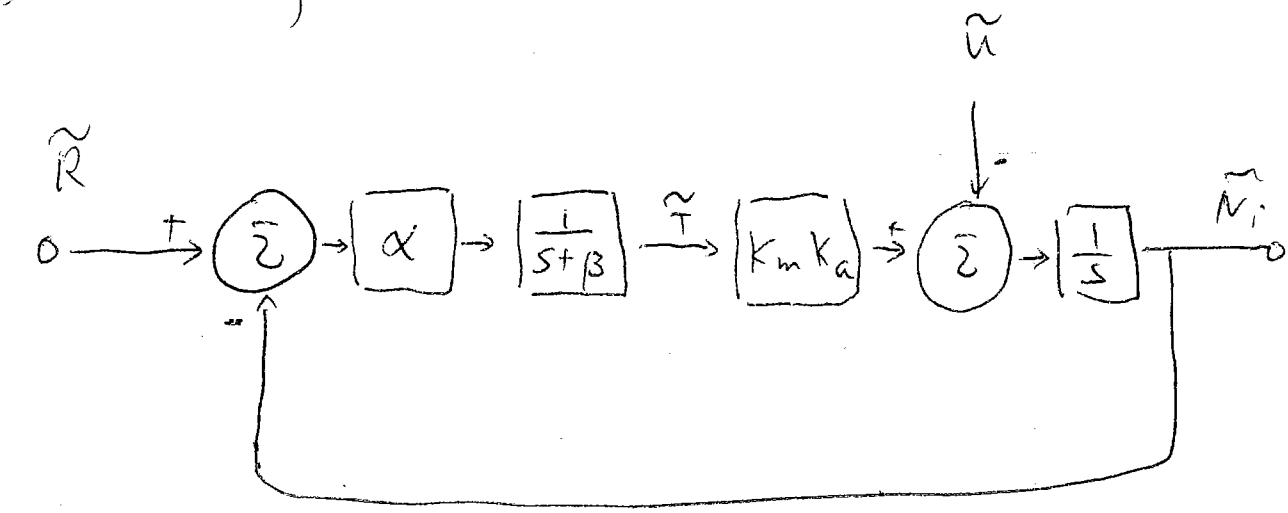
$$s\tilde{N}_i = k_m k_a \tilde{T} - \tilde{u}$$

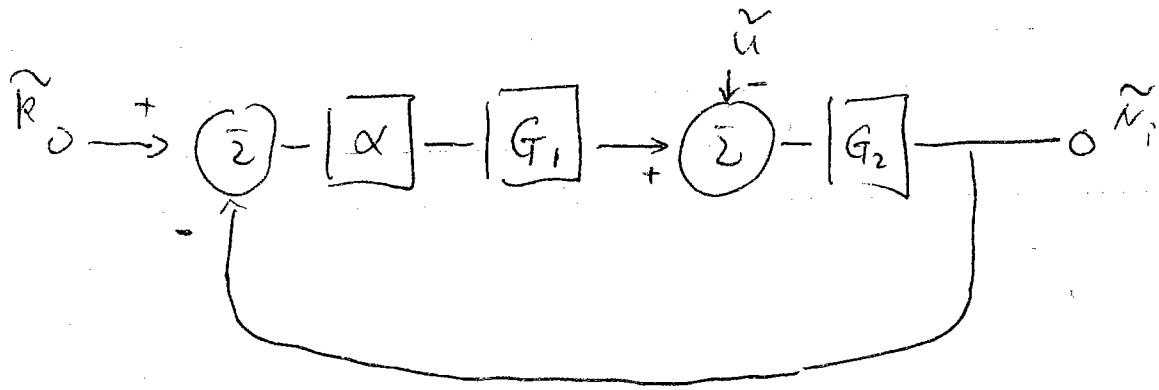
$$(s+\beta)\tilde{T} = \alpha(\tilde{R} - \tilde{N}_i)$$

$$\tilde{N}_i = \frac{1}{s}(k_m k_a \tilde{T} - \tilde{u})$$

$$\tilde{T} = \alpha \frac{1}{s+\beta}(\tilde{R} - \tilde{N}_i)$$

block diagram





$$G_1 = \frac{K_m K_a}{s+\beta} \qquad G_2 = \frac{1}{s}$$

to solve the loop equation

$$\left[\left(\tilde{R} - N_i \right) \alpha G_1 + \tilde{u} \right] G_2 = \tilde{N}_i$$

$$\tilde{R}\, \alpha G_1 G_2 - \tilde{u} G_2 = \tilde{N}_i \left(1 + \alpha G_1 G_2 \right)$$

$$\tilde{N}_i = \frac{\tilde{R}\, \alpha G_1 G_2 - \tilde{u} G_2}{1 + \alpha G_1 G_2}$$

$$= \frac{\tilde{R}\, \alpha \frac{K_m K_a}{s+\beta} \frac{1}{s} - \tilde{u} \frac{1}{s}}{1 + \alpha \frac{K_m K_a}{s+\beta} \frac{1}{s}}$$

$$\tilde{N}_i = \frac{\tilde{R}\,\alpha k_m k_a - \tilde{u}(s+\beta)}{s(s+\beta) + \alpha k_m k_a}$$

steady state

$$\tilde{R} = \frac{R}{s}$$
$$\tilde{u} = \frac{u}{s}$$

$$N_i(t \to \infty) = \lim_{s \to 0} s\tilde{N}_i$$

$$= s \cdot \frac{\frac{R}{s}\alpha k_m k_a - \frac{u}{s}(s+\beta)}{s(s+\beta) + \alpha k_m k_a}\Bigg|_{s \to 0}$$

$$= \frac{R\alpha k_m k_a - u\beta}{\alpha k_m k_a}$$

$$= R - \frac{u\beta}{\alpha k_m k_a}, \qquad \boxed{\beta = \beta_0 k_a}$$

$$= R - \frac{u\beta_0}{\alpha k_m} \rightarrow \text{not depend on } k_a \text{ external concentration}$$

stability is given by the poles of $\tilde{N}_i$ or roots of the characteristic equation

$$s^2 + s\beta + \alpha k_m k_a = 0$$

$$s_{1,2} = \frac{-\beta \pm \sqrt{\beta^2 - 4\alpha k_m k_a}}{2}$$

both roots on Left Hand plane $\rightarrow$ stable

features

external concentration

* perfect adaptation with respect to N_e
  but need fine tuned mechanism
  ↪ increase in uptake
  matches exactly the degradation
  increase
* not perfect adaptation w.r.t other parameters, e.g., usage rate
* increase gain, eg. α. decrease error, but may induce oscillations
* protein synthesis rate $\propto$ mRNA which can not jump $\propto (R - N_i)$

? Alternative model with perfect adaptation

1) instead of proportional feedback need integral feedback

model with integral feedback only ?

replace $\alpha (R - N_i)$

by $\alpha_I \int (R - N_i)\, dt$

Laplace transform $\frac{\alpha_I}{s} (\tilde{R} - \tilde{N}_i)$

just replace α by $\frac{\alpha_I}{s}$

$$\tilde{N}_i = \frac{\tilde{R}\,\frac{\alpha_I}{s}\,\frac{k_m k_a}{s+\beta}\,\frac{1}{s} - \tilde{u}\,\frac{1}{s}}{1 + \frac{\alpha_I}{s}\,\frac{k_m k_a}{s+\beta}\,\frac{1}{s}}$$

$$= \frac{\tilde{R}\,\alpha_I k_m k_a - \tilde{u}\,s(s+\beta)}{s^2(s+\beta) + \alpha_I k_m k_a}$$

th characteristic equation

$$s^3 + s^2\beta + \alpha_I k_m k_a = 0$$

with coefficient of s term 0

th system is always unstable

(must exist a root at RHP)

2) proposal 2

PI controller

replace $\alpha\,(R - N_i)$ by

$$\alpha_p (R - N_i) + \alpha_I \int (R - N_i)\,dt$$

replace α by $\alpha_p + \frac{\alpha_I}{s}$

$$\tilde{N}_i = \frac{\tilde{R}\left(\alpha_p + \frac{\alpha_I}{s}\right)\frac{k_m k_a}{s+\beta}\,\frac{1}{s} - \tilde{u}\,\frac{1}{s}}{1 + \left(\alpha_p + \frac{\alpha_I}{s}\right)\frac{k_m k_a}{s+\beta}\,\frac{1}{s}}$$

$$\tilde{N}_i = \frac{\tilde{R}\, k_m k_a (s\alpha_p + \alpha_I) - \tilde{u}\, s(s+\beta)}{s^2(s+\beta) + k_m k_a (s\alpha_p + \alpha_I)}$$

characteristic equation

$$s^3 + s^2\beta + k_m k_a \alpha_p s + k_m k_a \alpha_I = 0$$

in lecture 1, we worked out stability criterion

is that

$$\underbrace{k_m k_a \alpha_I}_{\text{const}} < \underbrace{k_m k_a \alpha_p \cdot \beta}_{\text{coeff of linear term}} \quad \text{coeff of second order term}$$

$$\alpha_I < \beta \alpha_p$$

th steady state

$N_i(t \to \infty) = R$ independent of all parameters

how to realize the PI controller

both the transcription factor Zap1 and the transporter Zrt1 are sensing zinc level

* two zinc fingers in Zap1 were implicated in zinc sensing → regulate activation domain

* th mechanism for Zrt1 zinc sensing less clear

(1) th integral part:

ZAP1 change activity according to N_i

ZAP1 activity $\propto (R - N_i)$

fast dynamics for ligand binding

transporter synthesis $\propto$ mRNA $\propto \int (R - N_i)\, dt$

accumulation of mRNA slow process

(2) th proportional part

degradation rate $= a + b N_i$

transporter sensing internal nutrient concentration

$$\frac{dN_i}{dt} = k_m k_a T - u$$

$$\frac{dT}{dt} = \alpha_I \int (R - N_i)\, dt - (a + b N_i) T$$

non linear eq.

but again $N_i(t \to \infty) = R$

steady state nothing is changing

linearize the equation around steady state $N_i = R + \delta N_i$

$T = T^*$

$$\frac{d\,\delta N_i}{dt} = k_m k_a T - u$$

$$\frac{dT}{dt} = -\alpha_I \int \delta N_i\, dt - b T^* \delta N_i - (a + bR) T$$

$$= -\alpha_I \int \delta N_i\, dt - \alpha_p \delta N_i - \beta T$$

$\alpha_p \equiv b T^*$, $\beta = a + bR$

stability condition

$$\alpha_I < \beta \alpha_p = (a + bR) b T^*$$

however T^* is decreasing with increased external concentration

$\longrightarrow$ higher external concentr.

less stable

△ An interesting prediction is that the transporter is sensing internal concentration instead of external concentration

(1) a number of predictions can be tested

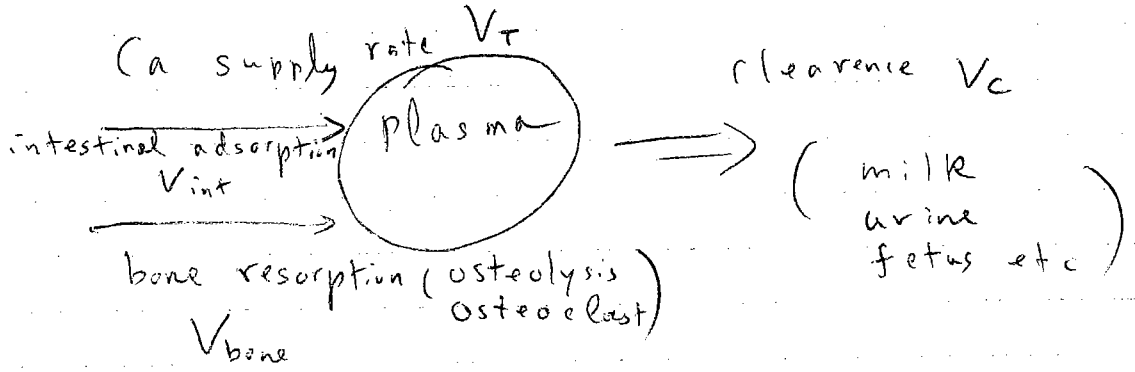
* time scale for homeostasis < mRNA life time for transporter
* transporter senses internal concentration
* stability decrease as external concentration increase

(2) a key question is what sets set point for transcription factor response ?

El-Samad et. al

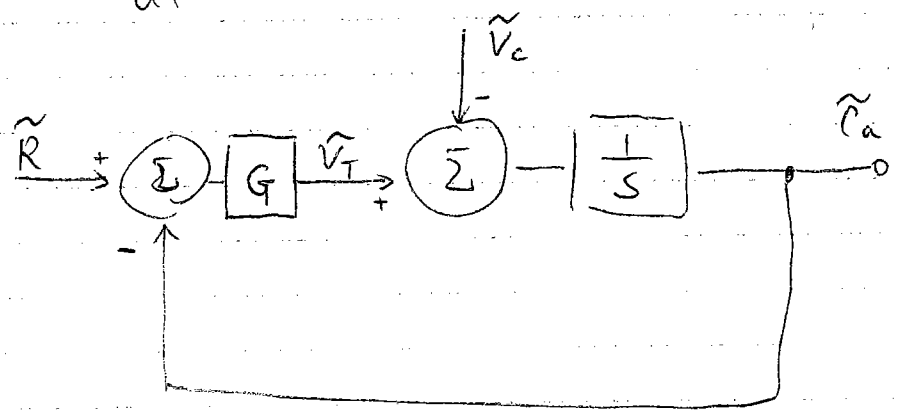
modeling

Example : Calcium homeostasis



$$V_T = V_{bone} + V_{int}$$

$$\frac{d(Ca)}{dt} = V_T - V_c$$



standard model by Ramberg et. al.

feedback proportional : $V_T = k_p (R - Ca)$

$$G = k_p$$

Solve the loop equation

$$(\tilde{R} - \tilde{C}_a) G/s - \tilde{V}_c/s = \tilde{C}_a$$

$$\tilde{C}_a = \frac{\tilde{R}\, G/s - \tilde{V}_c/s}{1 + G/s}$$

G/s → loop gain

for proportional feedback

$$G = k_p$$

$$\tilde{C_a} = \frac{\tilde{R} k_p - \tilde{V_c}}{s + k_p}$$

for const R and V_c

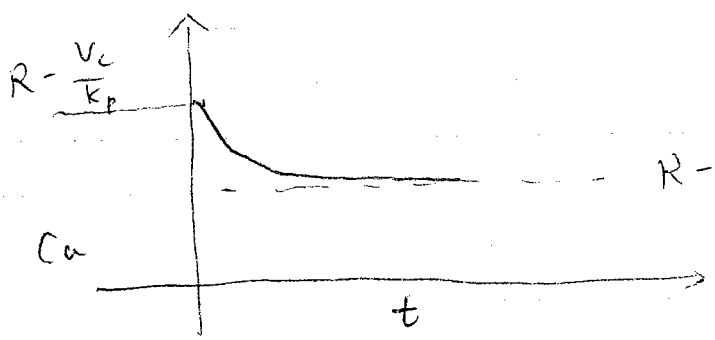
$$\tilde{R} = \frac{R}{s}, \quad \tilde{V_c} = \frac{V_c}{s}$$

Steady state

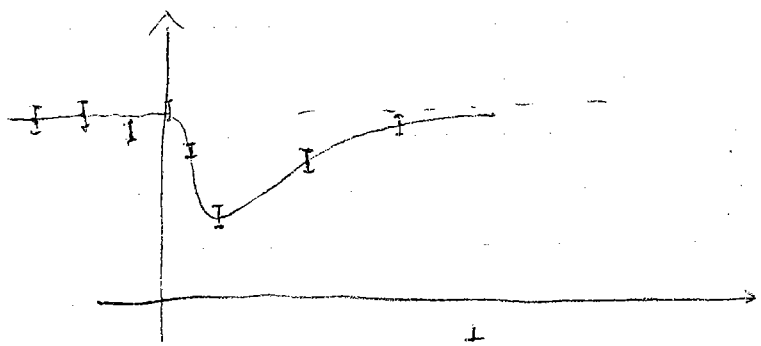
$$C_a(t \to \infty) = \lim_{s \to 0} s \tilde{C_a} = \frac{R k_p - V_c}{k_p} = R - \frac{V_c}{k_p}$$

Thus a change in clearence rate lead to a change of steady state level

the pole is $-k_p$, expurential decay with time const $\tau = \frac{1}{k_p}$



real observation



perfect adaptation shape of the curve different

El-Samad et. al. proposed a PI controller model.

$$V_T = k_p (R - C_a) + k_i \int_0^t (R - C_a)\, dt$$

$$G = k_p + k_i/s$$

$$\tilde{C}_a = \frac{\tilde{R}\, G/s - \tilde{V}_c/s}{1 + G/s}$$

$$= \frac{\tilde{R}\,(k_p + k_i/s)\frac{1}{s} - \tilde{V}_c/s}{1 + (k_p + k_i/s)/s}$$

$$= \frac{\tilde{R}\,(k_p s + k_i) - \tilde{V}_c\, s}{s^2 + k_p s + k_i}$$

$$\tilde{R} = \frac{R}{s} \qquad \tilde{V}_c = \frac{V_c}{s}$$

steady state

$$C_a(t \to \infty) = \lim_{s \to 0} s\,\tilde{C}_a = \frac{R\,(k_p s + k_i) - V_c\, s}{s^2 + k_p s + k_i}\Bigg|_{s \to 0}$$

$$= R$$

perfect adaptation

stability

roots: $s^2 + k_p s + k_i = 0$

$$s = \frac{-k_p \pm \sqrt{k_p^2 - 4k_i}}{2}$$

always stable if $k_p^2 > 4k_i$

oscillatory

realization of PI controller by hormones, two hormone scenario

$V_T = V_A + V_B$

$V_A \propto$ [Hormone A] $\propto$ error

$V_B \propto$ [Hormone B]

$\frac{d}{dt}$ [Hormone B] $\propto$ [Hormone A]

$V_T = k_p \text{Error} + k_i \int \text{Error}$

parathyroid gland $\rightarrow$ [PTH] $\propto$ Error

$\hookrightarrow \propto$ bone resorption

$1,25(OH)_2D \propto$ intestine adsorption

$25(OH)D \xrightarrow{PTH} 1,25(OH)_2D$

$\frac{d}{dt}$ [$1,25(OH)_2D$] $\propto$ [PTH]