the wisdom of the body revisited

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Outline

- Cannon's Homeostasis
- Mathematical models of homeostasis
- The power of integral action
- Integral control as a therapeutic

THE WISDOM OF THE BODY

BY

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1932

- The body—a system composed of fragile material—effectively operates in highly uncertain regimes.
- How does a body remain constancy despite the adverse forces that surround it?
- What are general principles to maintain this constancy?

The constant conditions which are maintained in the body might be termed *equilibria*. That word, however, has come to have fairly exact meaning as applied to relatively simple physico-chemical states, in closed systems, where known forces are balanced. The coördinated physiological processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings—involving, as they may, the brain and nerves, the heart, lungs, kidneys and spleen, all working coöperatively—that I have suggested a special designation for these states, *homeostasis*. The word does not imply something set and immobile, a stagnation. It means a condition—a condition which may vary, but which is relatively constant.

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Treatment of clotting disorders with blood thinners

Insulin discovery, treatment of diabetes

Cybernetics!

Calcium Homeostasis - a view from 1932

- Calcium used both for bone growth, muscle signalling, and blood coagulation.
- Calcium concentration in blood is *constant*. Too little cause muscle convulsions. Too much causes blood thickening
- Regulated by parathyroid gland?
- Calcium stored in bones and resorbed when needed.
- Vitamin D helps calcium be absorbed in the intestine.

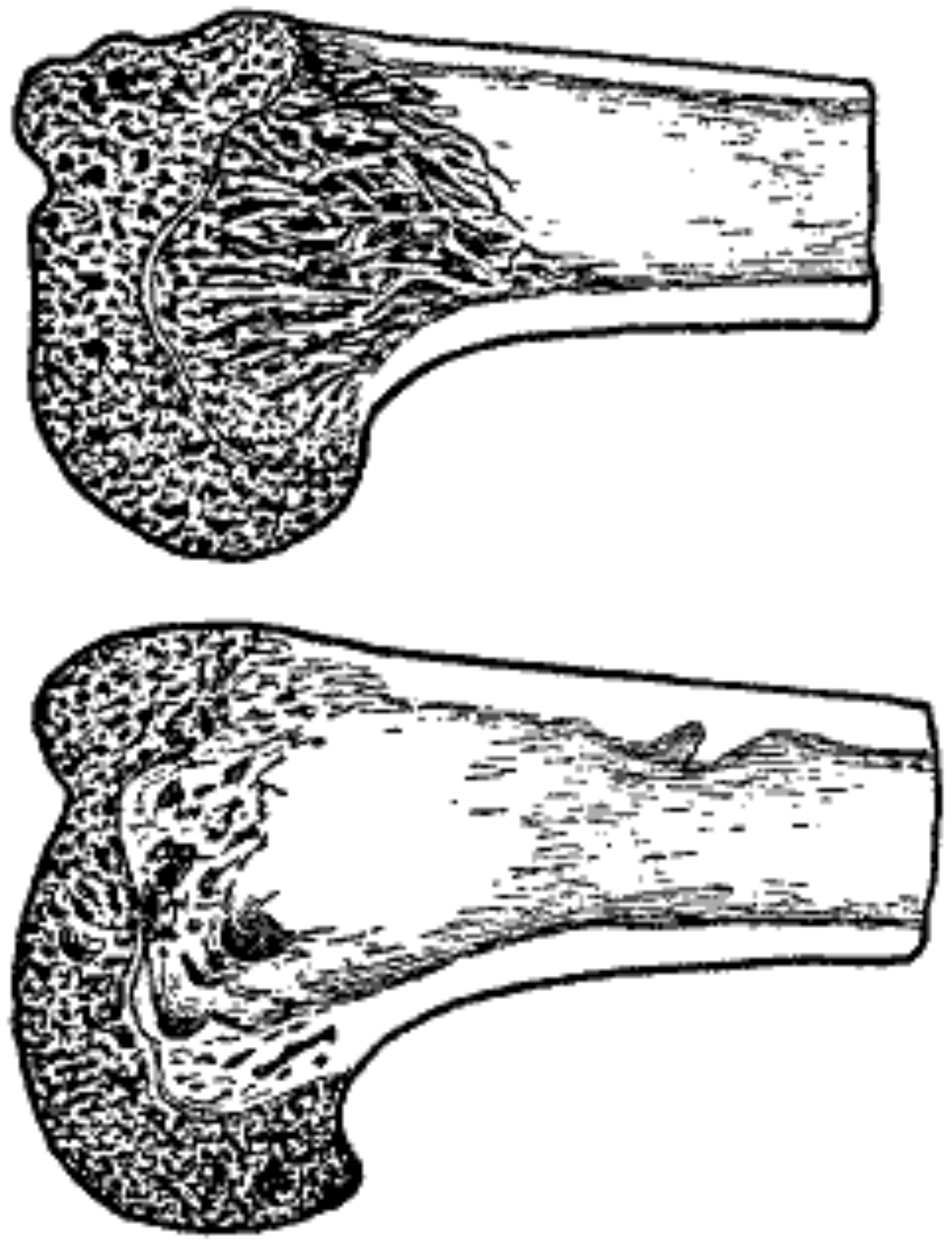
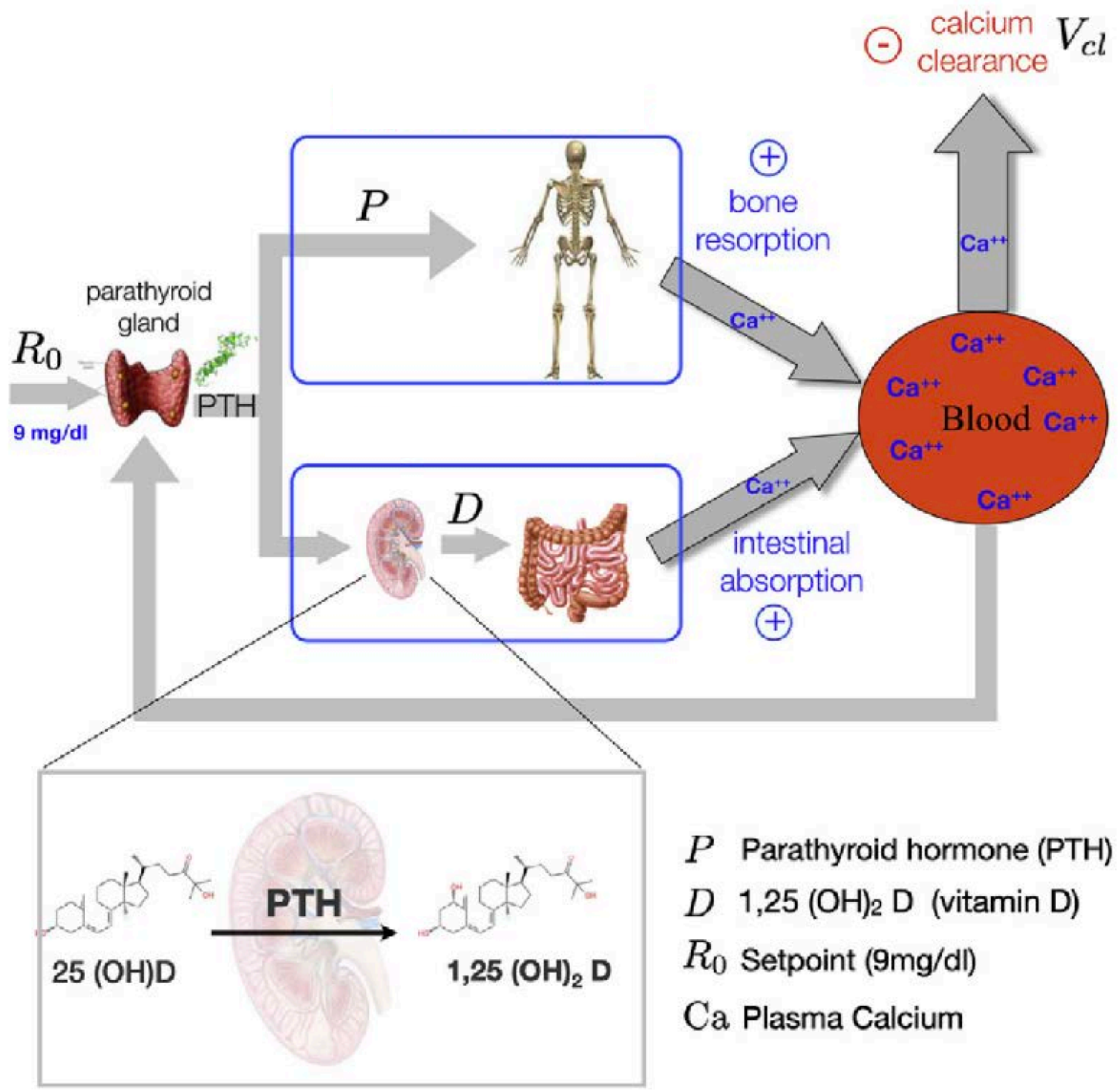
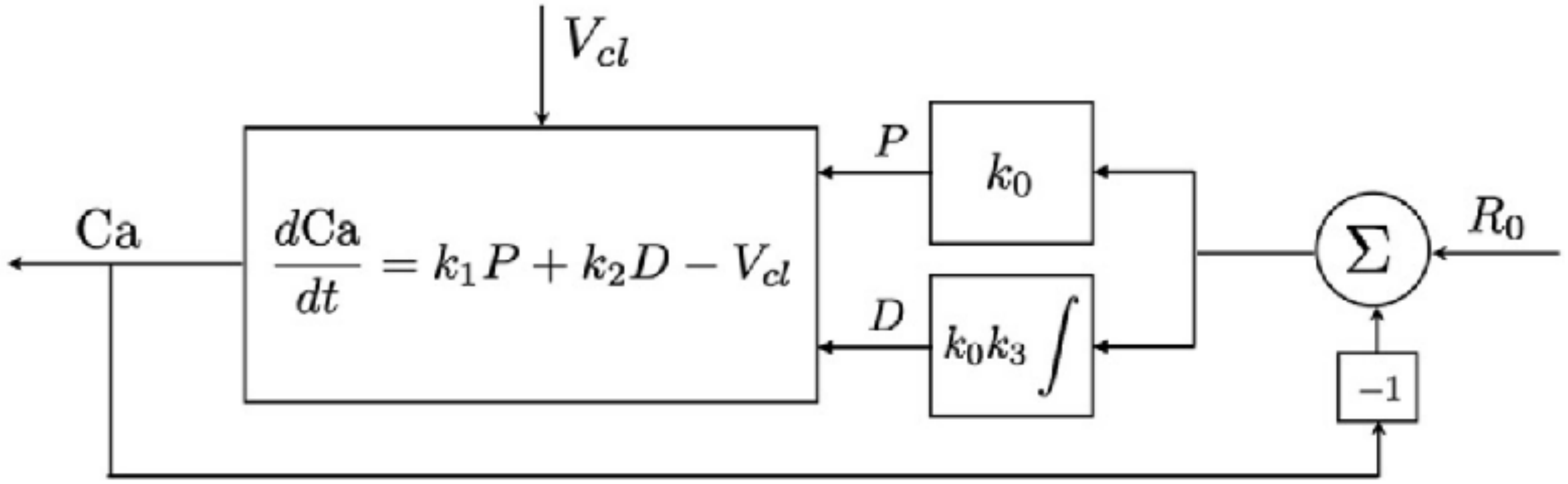


Fig. 26. Drawings from a photograph showing the effects of diet on the trabeculae in the humeri of a cat. The upper humerus, removed after a high calcium diet, contains many more trabeculae than its opposite member which was taken after a low calcium diet.

From Khammash 2021

Calcium Homeostasis





$$e_t := R_0 - \mathrm{Ca}_t$$

$$P_t = k_0(R_0 - \mathrm{Ca}_t) \longrightarrow P_t = k_0 e_t$$

$$D_{t+1} = D_t + k_3 P_t \longrightarrow D_t = k_3 k_0 \sum_{j=0}^{t-1} e_j$$

$$\mathrm{Ca}_{t+1} = \mathrm{Ca}_t + k_1 P_t + k_2 D_t - V_t$$

$$u_t := k_1 P_t + k_2 D_t$$

Proportional Integral Control

$$\mathrm{Ca}_{t+1} = \mathrm{Ca}_t + u_t - V_t$$

$$u_t = (k_0 k_1)\, e_t + (k_0 k_2 k_3) \sum_{j=0}^{t} e_j$$

$$e_t = R_0 - \mathrm{Ca}_t$$

Integral Action

- Consider the proportional integral (PI) controller

$$u_t = k_P e_t + k_I \sum_{j=0}^{t-1} e_j \quad = k_P e_t + k_I s_t + t \cdot k_I e_\infty$$

- Assume that all the signals converge to constant values.

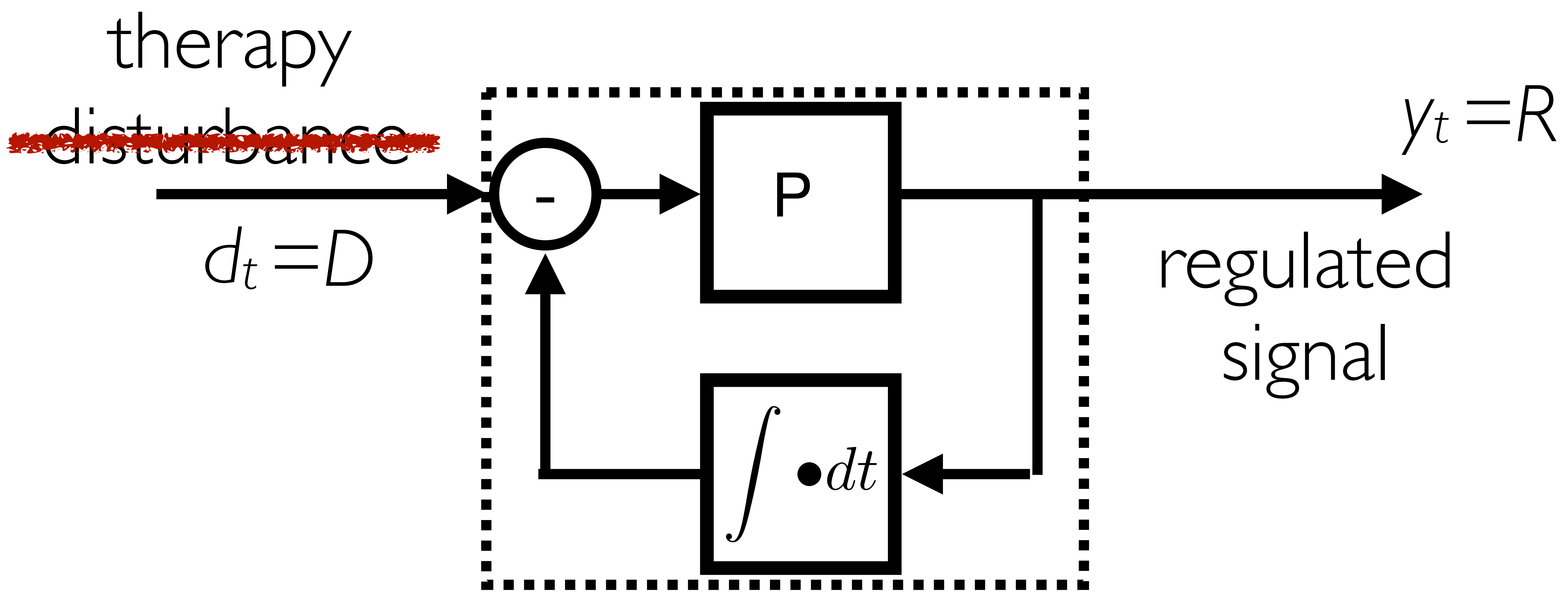
$$e_t \to e_\infty \qquad u_t \to u_\infty \qquad s_t := \sum_{j=0}^{t-1} (e_j - e_\infty) \to s_\infty$$

- Then e_∞=0.

A controller with integral action will always yield the correct steady state provided that a steady state exists.

adapts to changing disturbances

Perfect Adaptation: A system regulates some signal to a constant for any constant disturbance



For *any* value of *D*, the output converges to the *same* value of *R*.

- For linear systems, integral control is necessary and sufficient for perfect adaptation.
- For nonlinear systems, internal integrator is *sufficient*. This points a path for intervention.

From Khammash 2021

General Adaptation Syndrome (GAS)

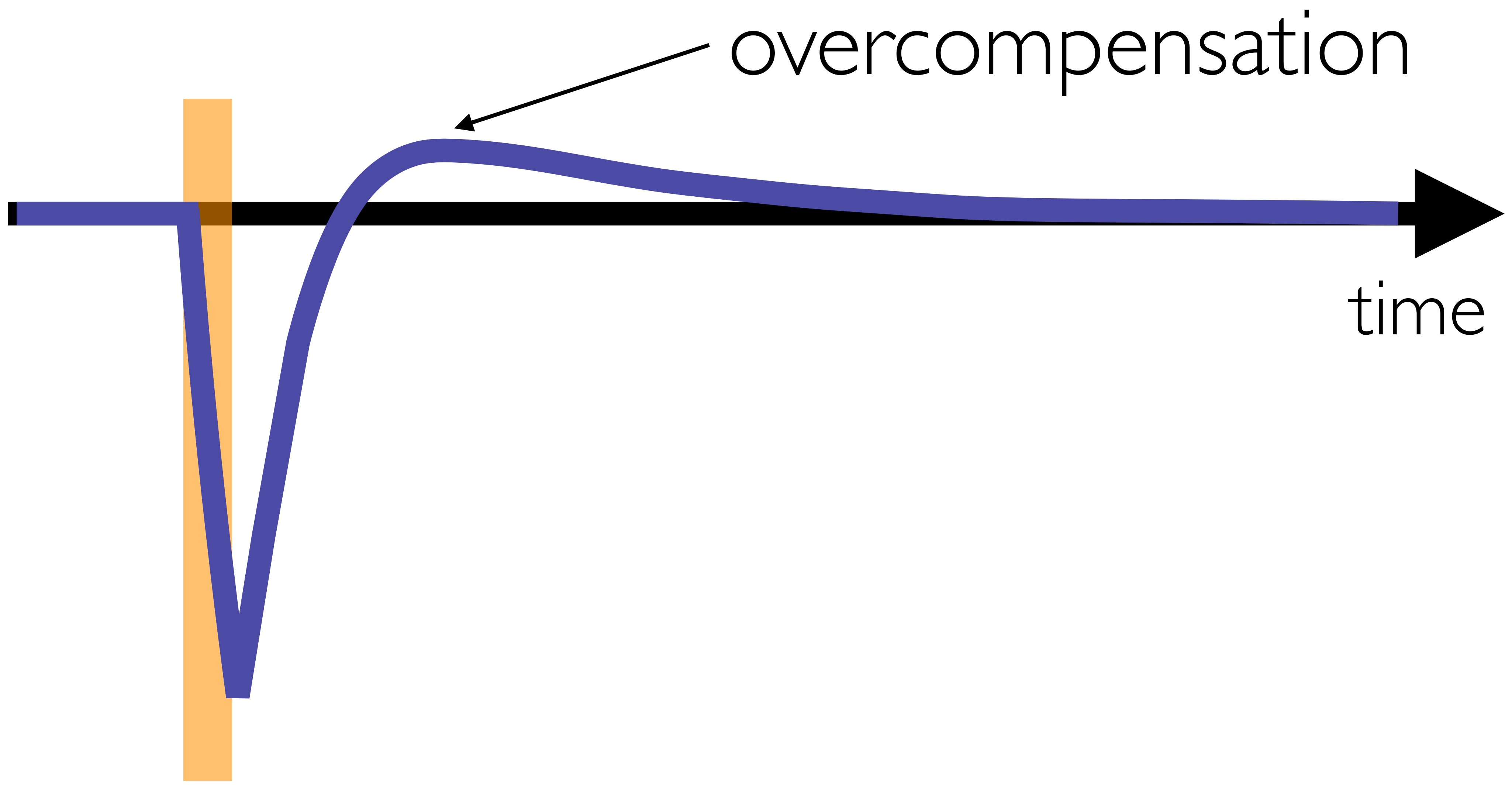
Linear model

$$y_t = \sum_{s=0}^{t} g_s d_{t-s} = (g * d)_t$$

g_t is the *impulse repsonse* or *shock response*

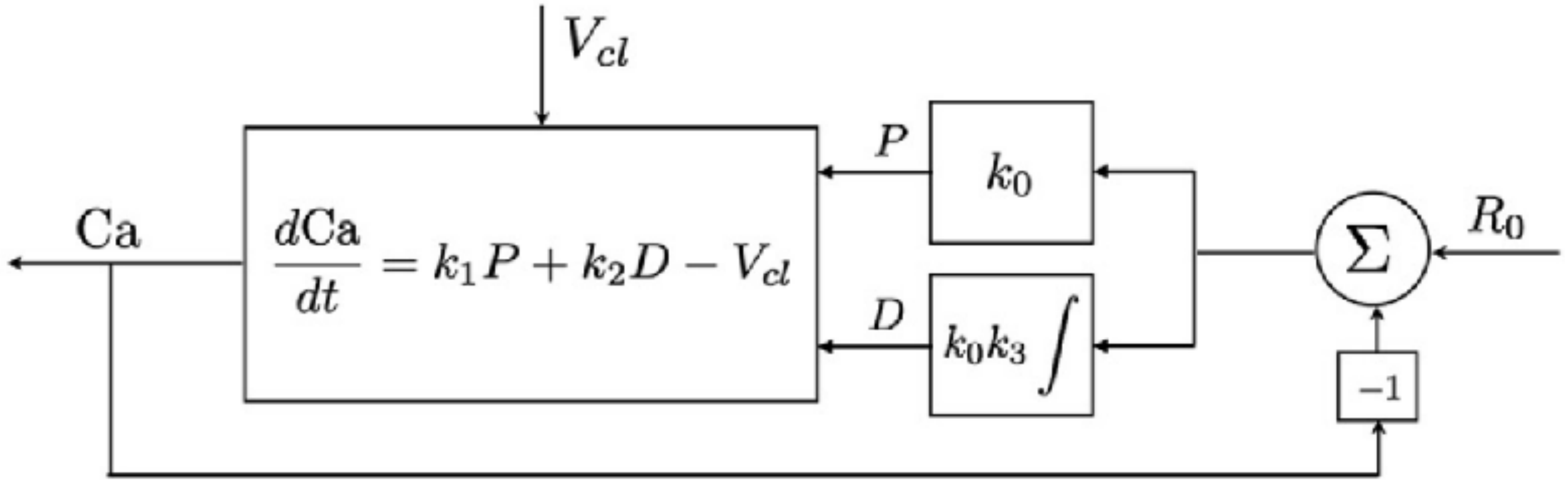
Perfect adaptation

$$d_t = D \implies y_\infty = 0$$

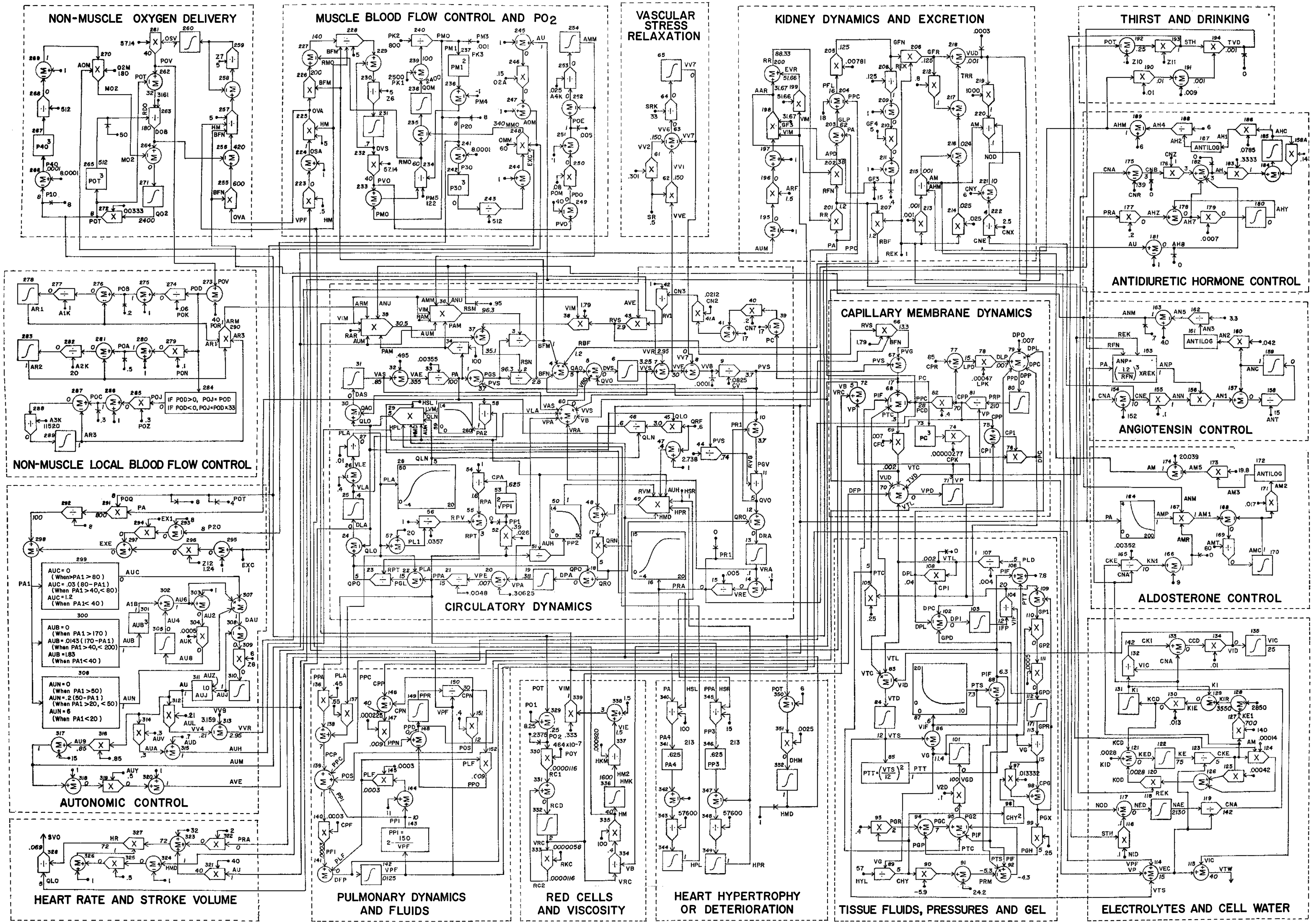


$$\sum_{s=0}^{\infty} g_s = 0$$

Response to a shock must overcompensate

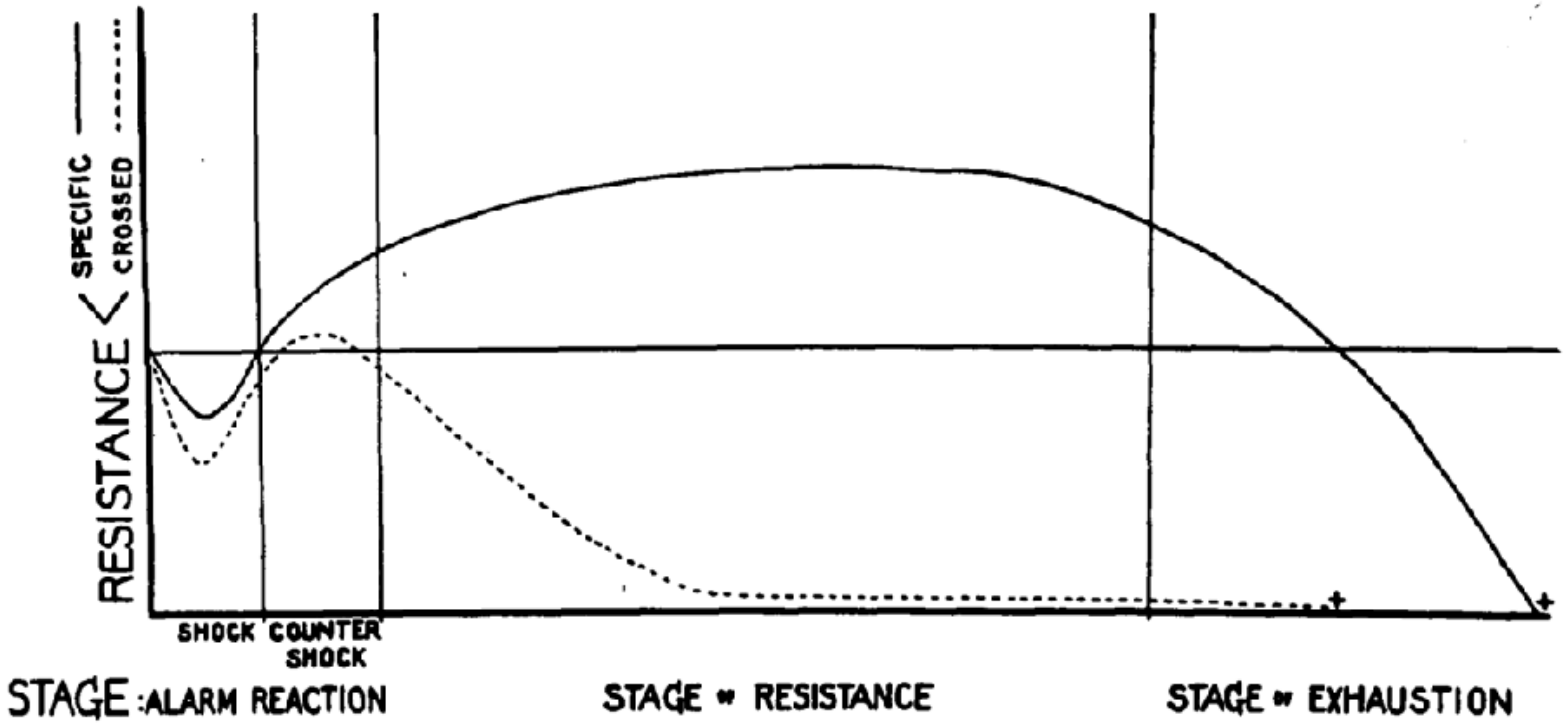


V_{cl}
P
k_0
Ca
$\frac{d\mathrm{Ca}}{dt} = k_1 P + k_2 D - V_{cl}$
Σ
R_0
D
$k_0 k_3 \int$
-1


NON-MUSCLE OXYGEN DELIVERY
MUSCLE BLOOD FLOW CONTROL AND PO2
VASCULAR STRESS RELAXATION
KIDNEY DYNAMICS AND EXCRETION
THIRST AND DRINKING
ANTIDIURETIC HORMONE CONTROL
NON-MUSCLE LOCAL BLOOD FLOW CONTROL
CAPILLARY MEMBRANE DYNAMICS
ANGIOTENSIN CONTROL
CIRCULATORY DYNAMICS
AUTONOMIC CONTROL
ALDOSTERONE CONTROL
HEART RATE AND STROKE VOLUME
PULMONARY DYNAMICS AND FLUIDS
RED CELLS AND VISCOSITY
HEART HYPERTROPHY OR DETERIORATION
TISSUE FLUIDS, PRESSURES AND GEL
ELECTROLYTES AND CELL WATER

General Adaptation Syndrome (GAS)

- Selye (1956)



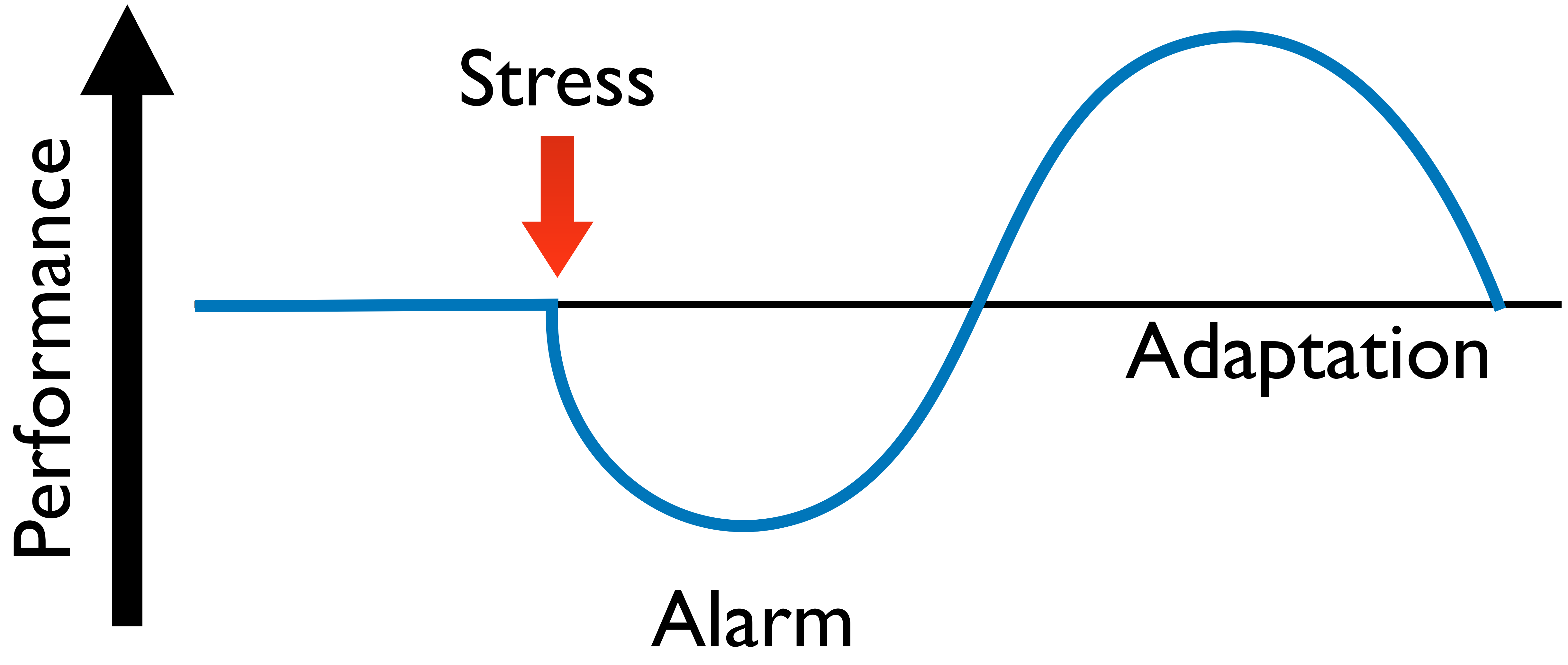
- Pattern of resistance to shock
- After first shock, more vulnerable. Then more resistant
- Transient shock recovers faster than adaptations decay

Processes working to maintain homeostasis overshoot too.

Aggregate properties of homeostatic processes overshoot, but need not reject disturbances.

Adaptation Therapy: Progressive Overload

- GAS Selye (1956)



Principle of progressive overload:

- Add a new stimulus to promote adaptation
- Fatigue recovers faster than adaptations decay
- If we consistently introduce new stimuli after sufficient recovery, performance levels increase over time.


ROGUE


SBD


ARNOLD
MHP
ROGUE


ROGUE
GIRLS
WHO
EAT

Strength Training

Coach Ben's Program

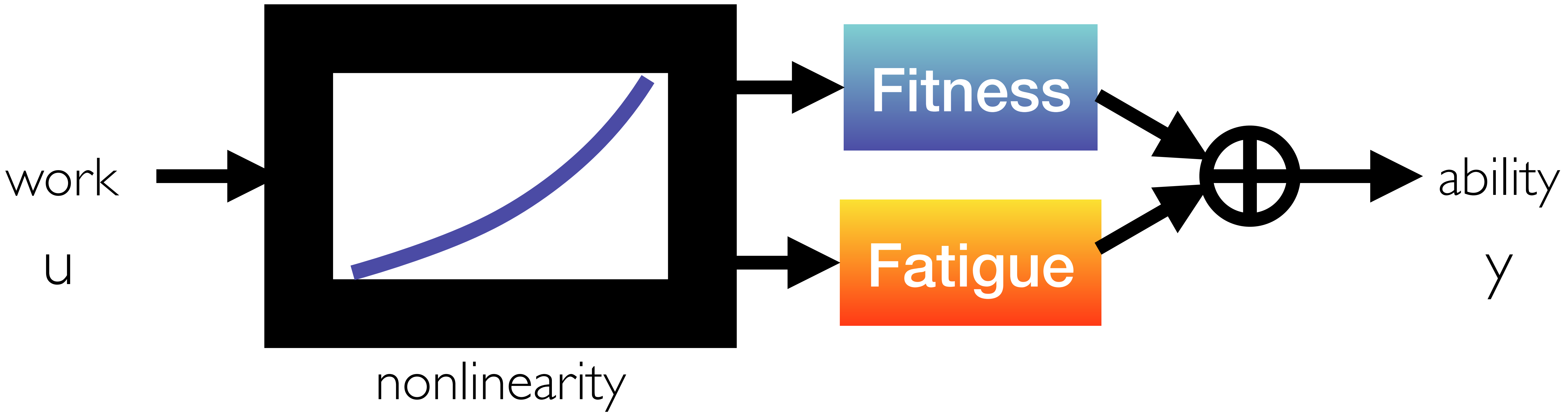
	M	W	F
Week 1	3x5@135#	3x5@145#	3x5@155#
Week 2	3x5@165#	3x5@175#	3x5@185#
Week 3	3x5@195#	3x5@205#	3x5@210#
Week 4	3x5@215#	3x5@220#	3x5@225#

Linear Progression

Simplest example of progressive overload

Fitness-Fatigue Model

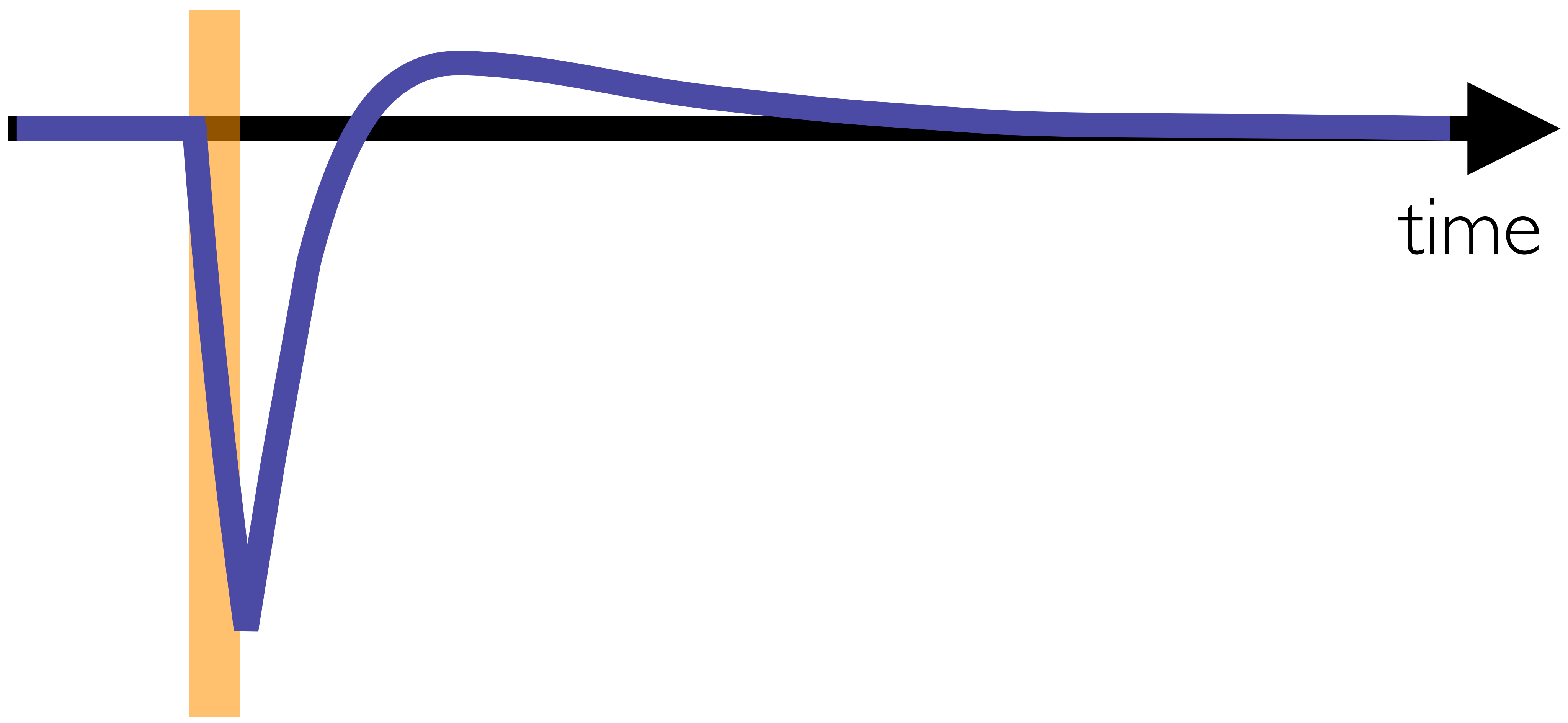
Bannister et al. (1976)



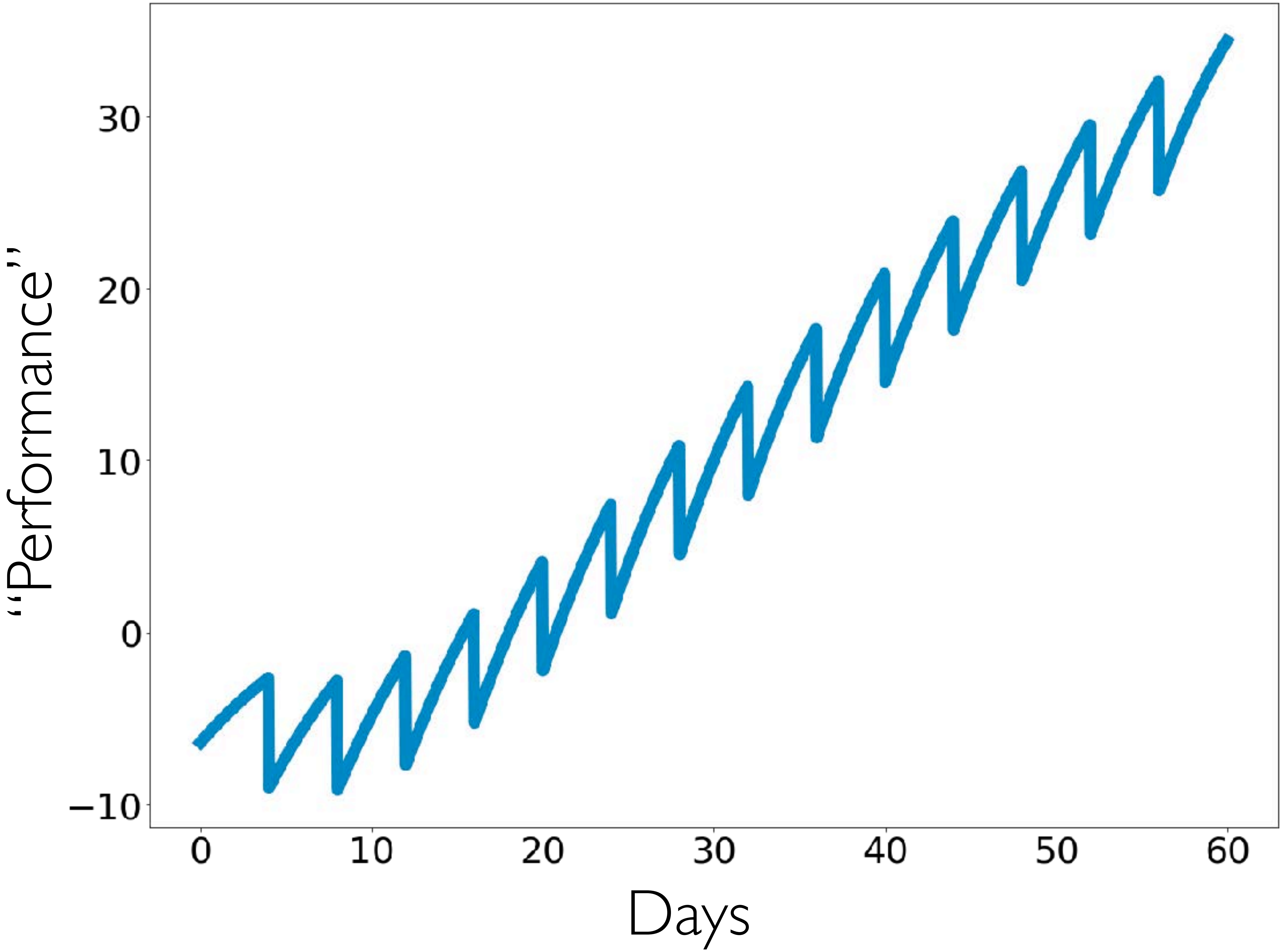
$$y[t] = y[0] + c_{fi} \sum_{s=0}^{t} a_{fi}^{t-s} b_{fi}(u[s]) - c_{fa} \sum_{s=0}^{t} a_{fa}^{t-s} b_{fa}(u[s])$$

Fitness

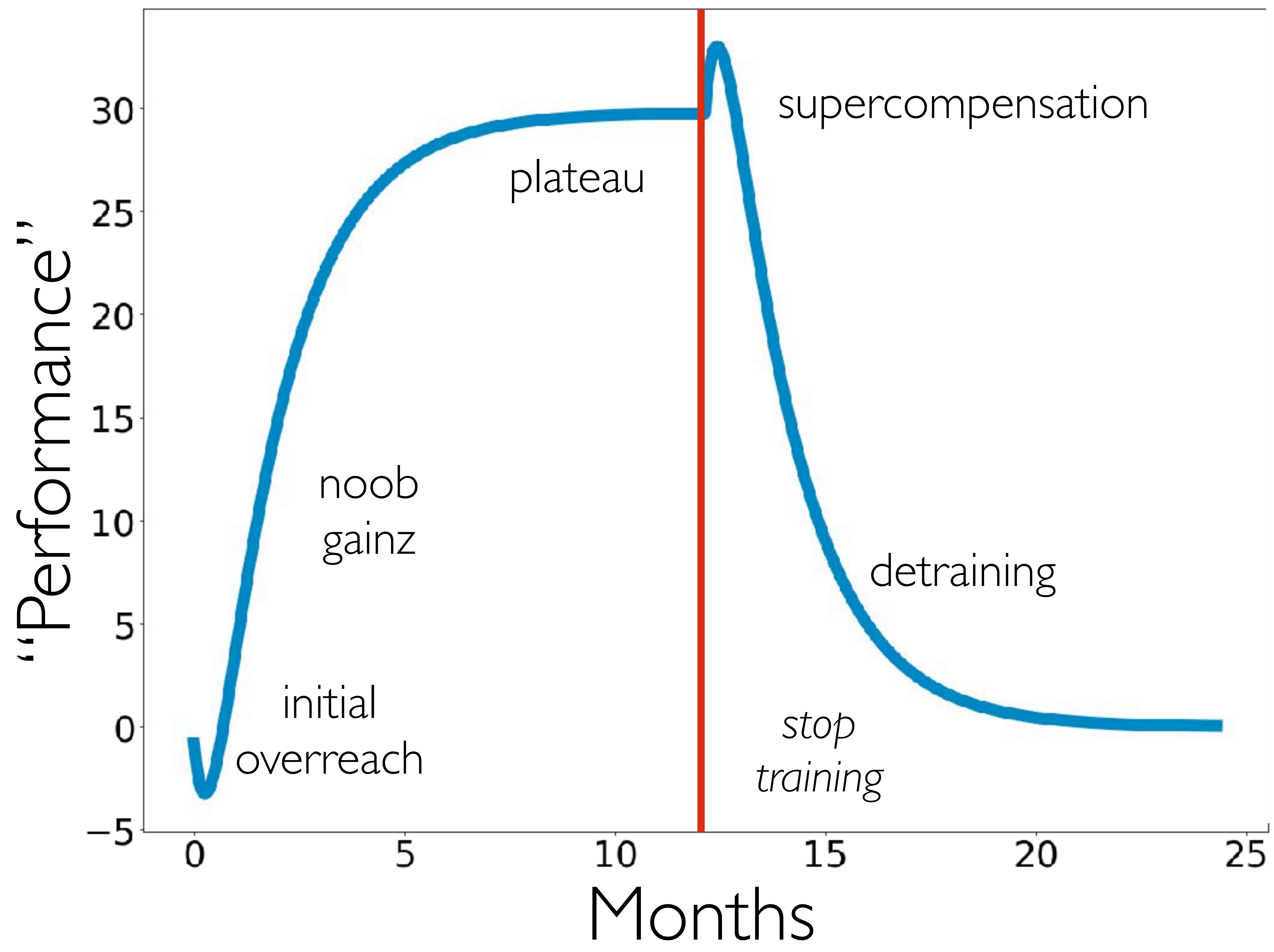
Fatigue



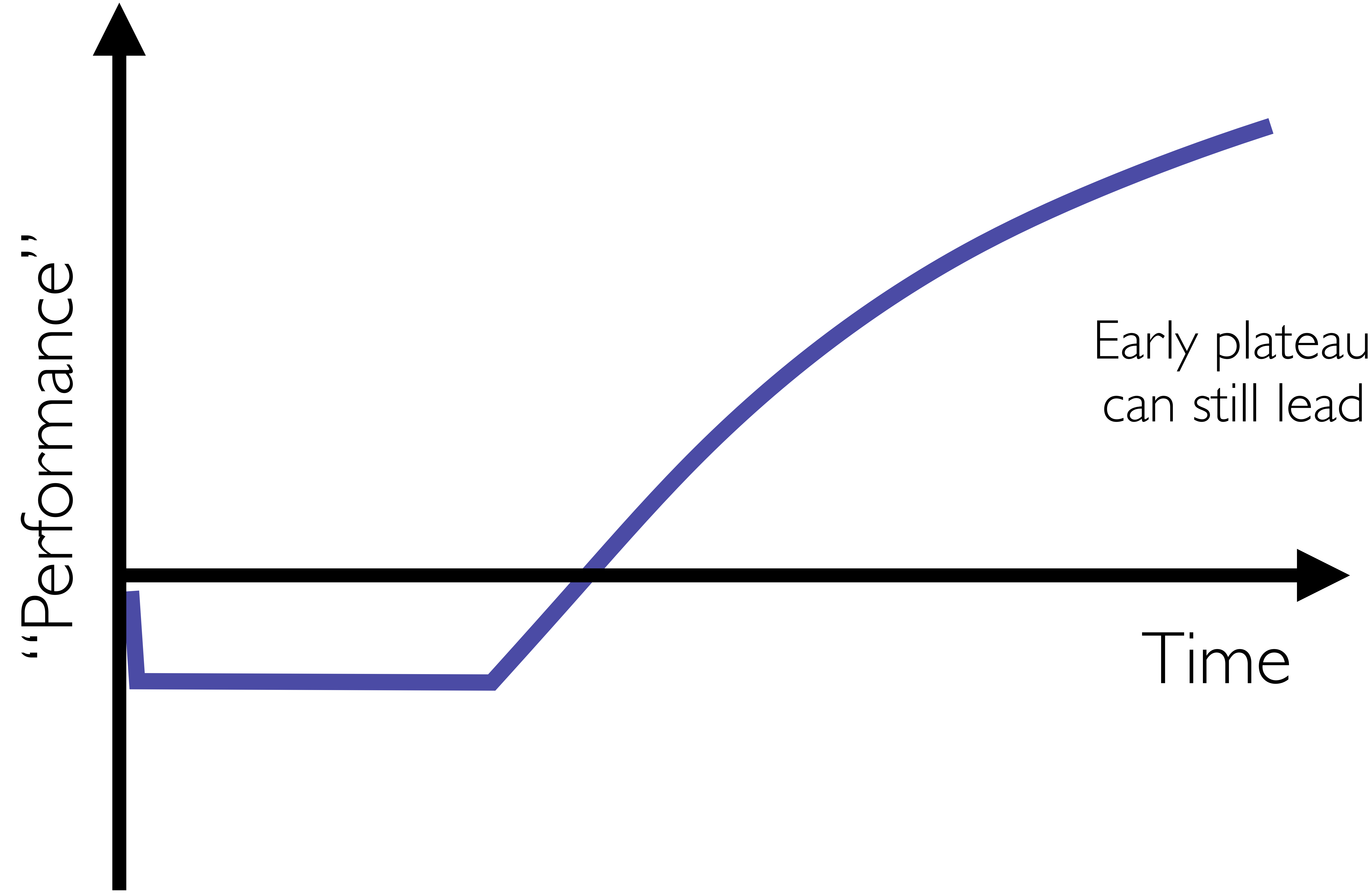
Progressive Overload



Dynamics of training

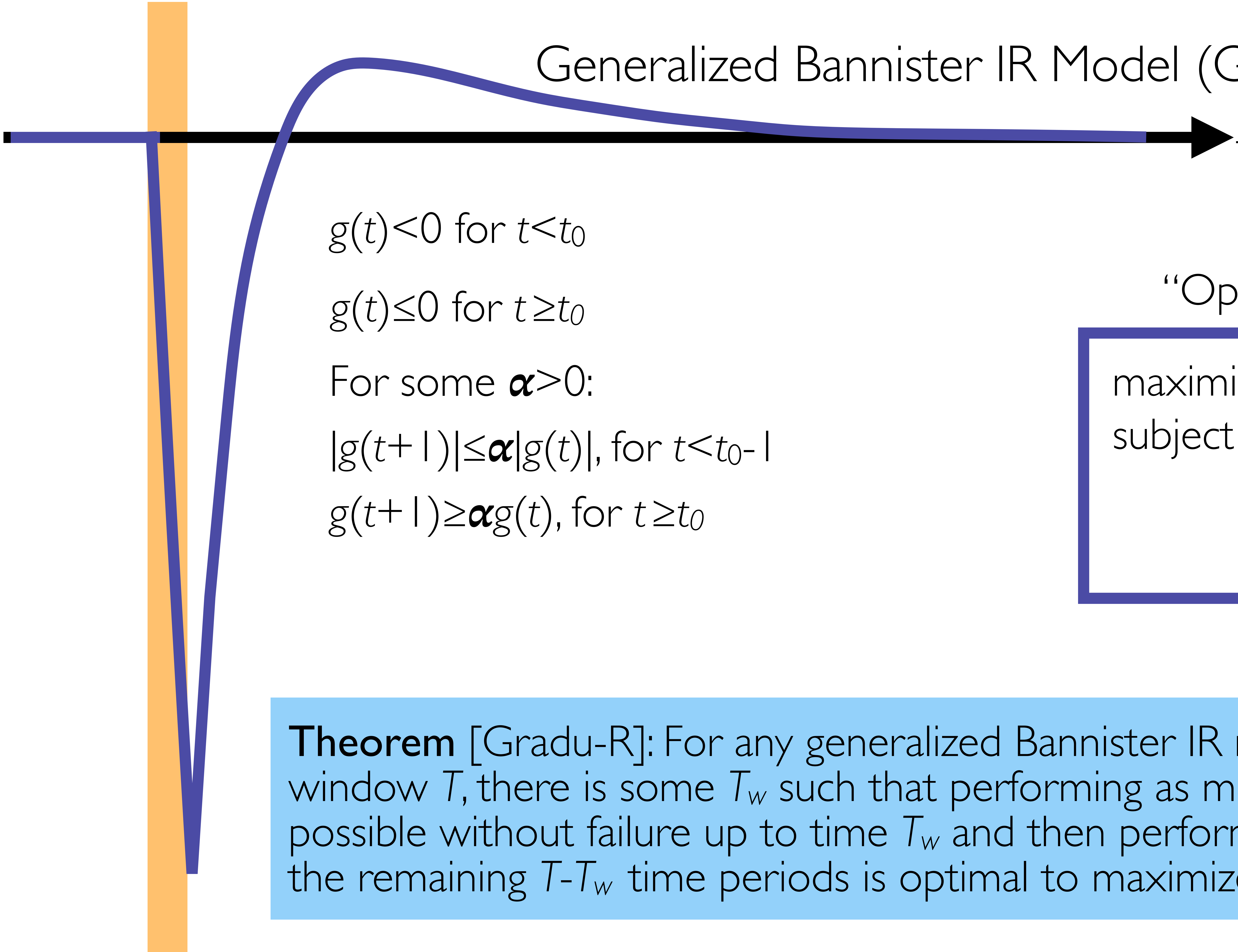


Dynamics of Overreaching



Early plateaus of overreaching can still lead to improvement

Generalized Bannister IR Model (Gradu-R)



$g(t)<0$ for $t<t_0$

$g(t)\leq 0$ for $t\geq t_0$

For some $\boldsymbol{\alpha}>0$:

$|g(t+1)|\leq\boldsymbol{\alpha}|g(t)|$, for $t<t_0-1$

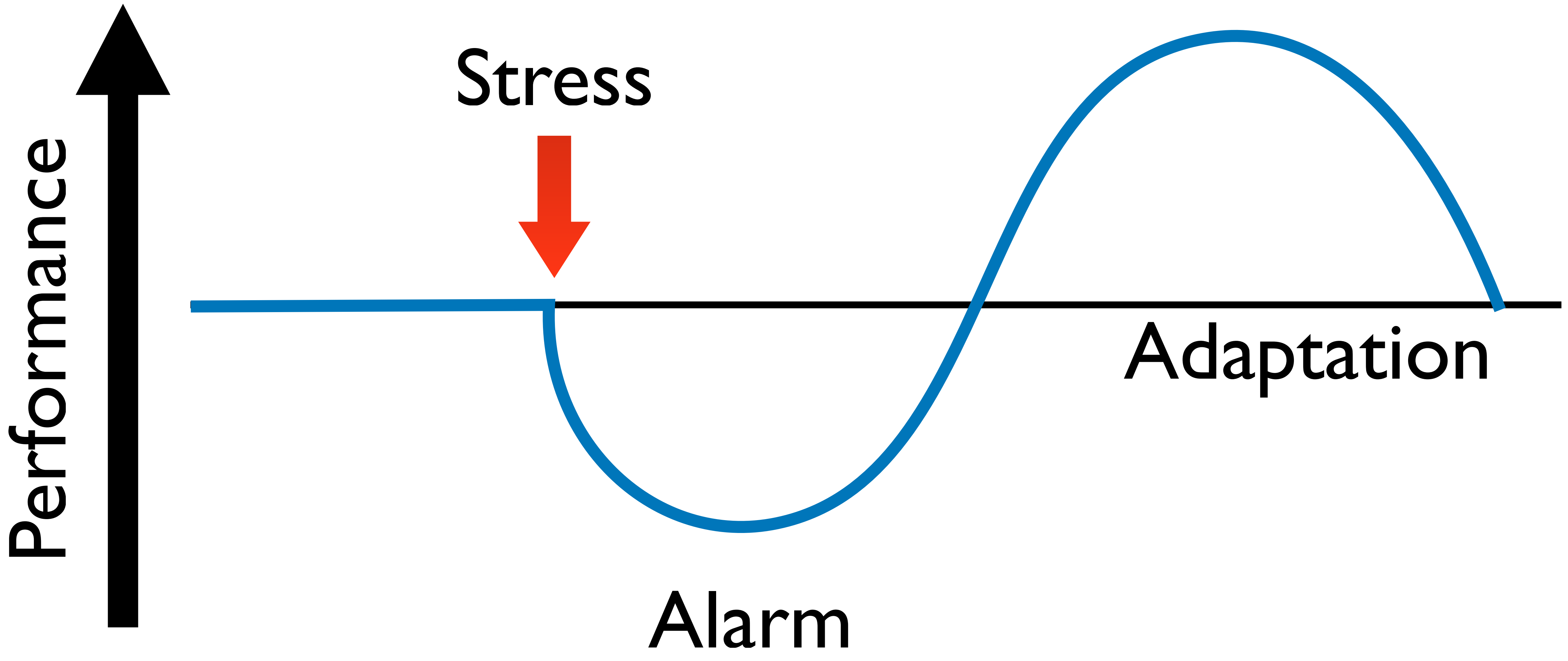
$g(t+1)\geq\boldsymbol{\alpha}g(t)$, for $t\geq t_0$

"Optimal training"

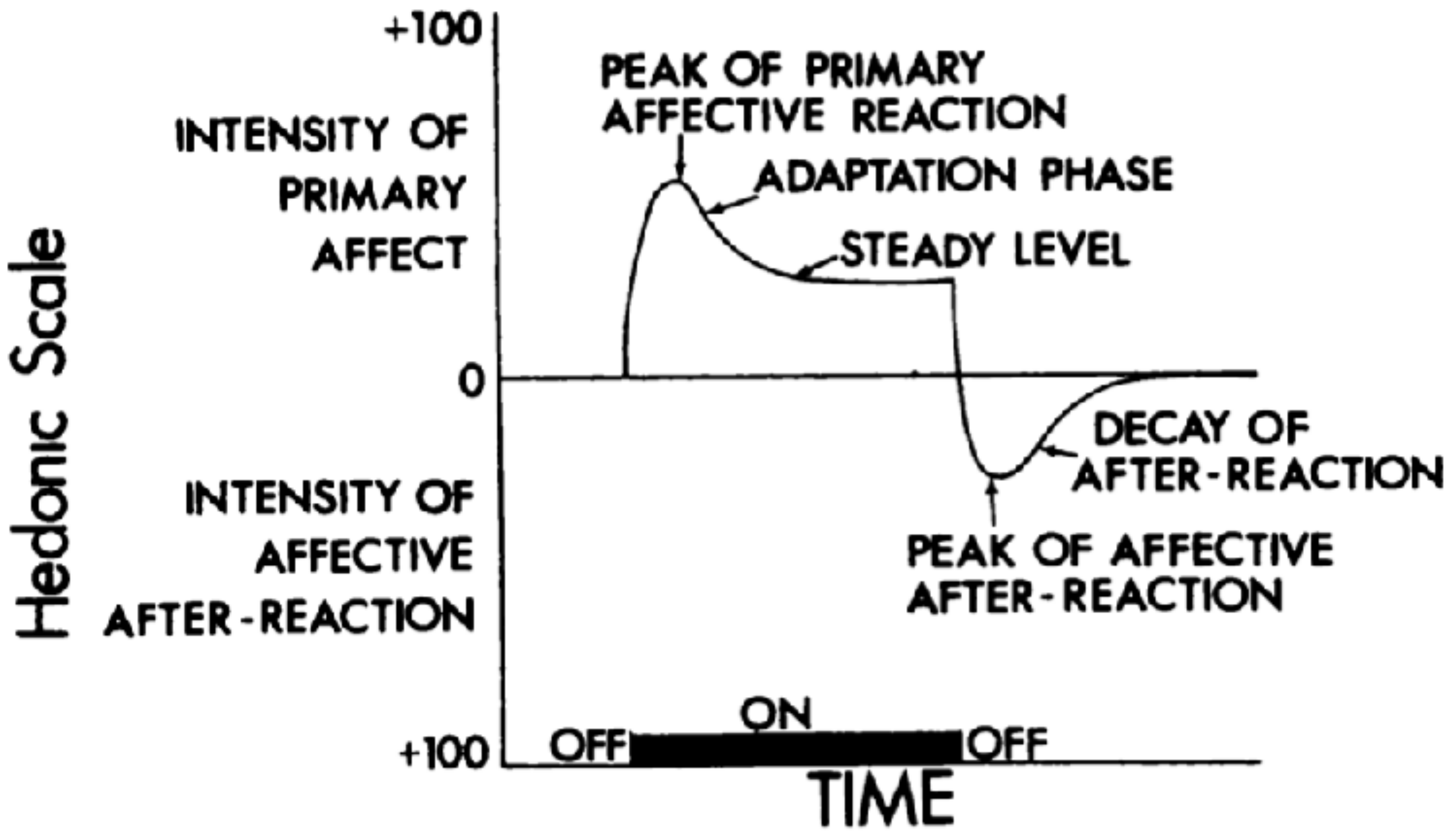
$$
\begin{array}{ll}
\text{maximize} & y_T \\
\text{subject to} & y_t \geq y_{\min} \\
 & 0 \leq u \leq B \\
 & y = g * u
\end{array}
$$

Theorem [Gradu-R]: For any generalized Bannister IR model and training window T, there is some T_w such that performing as much work as possible without failure up to time T_w and then performing no work for the remaining T-T_w time periods is optimal to maximize ability.

GAS (Selye 1956)

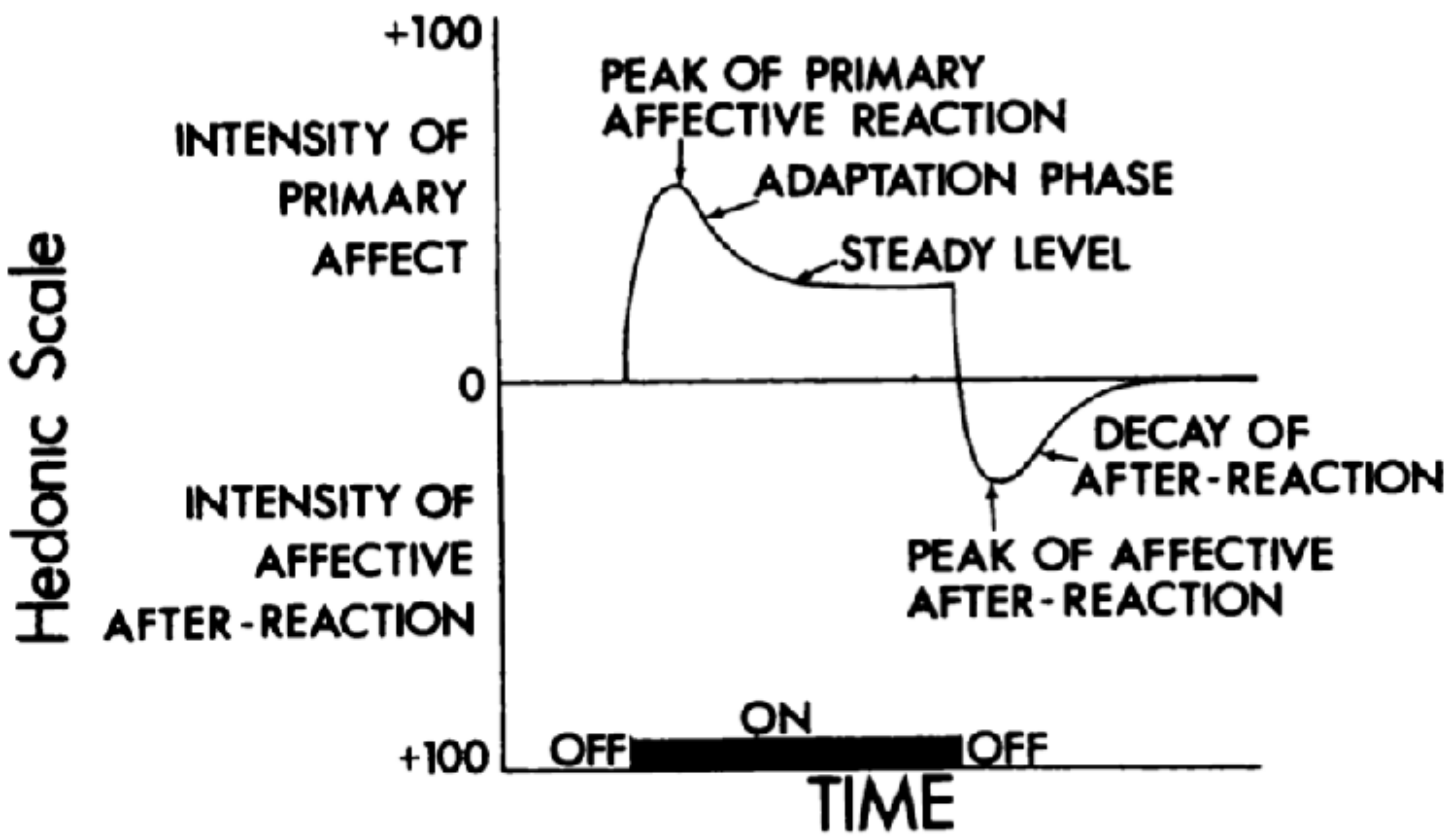


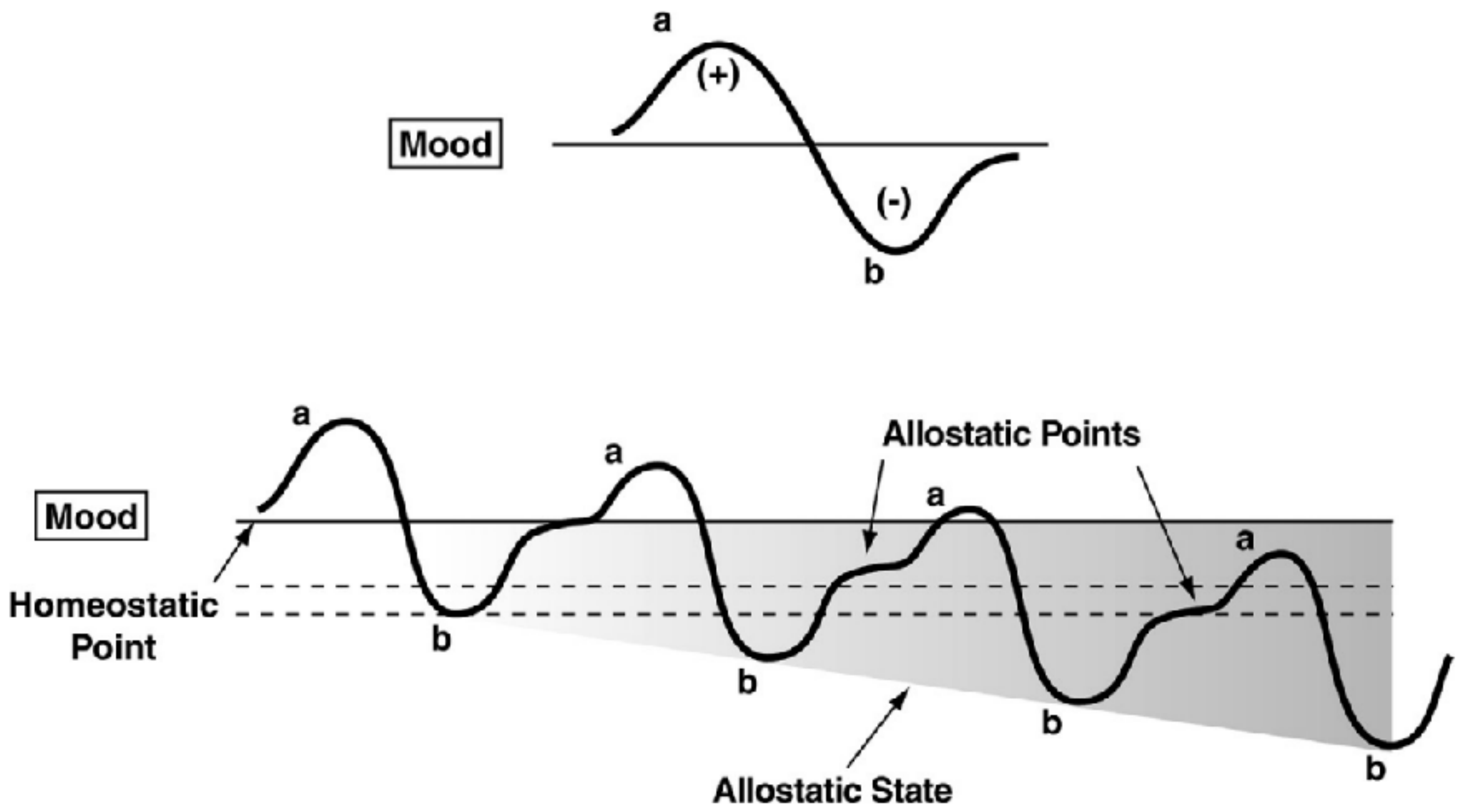
Opponent process (Solomon 1980)



Dynamics of addictive substances

Opponent process (Solomon 1980)





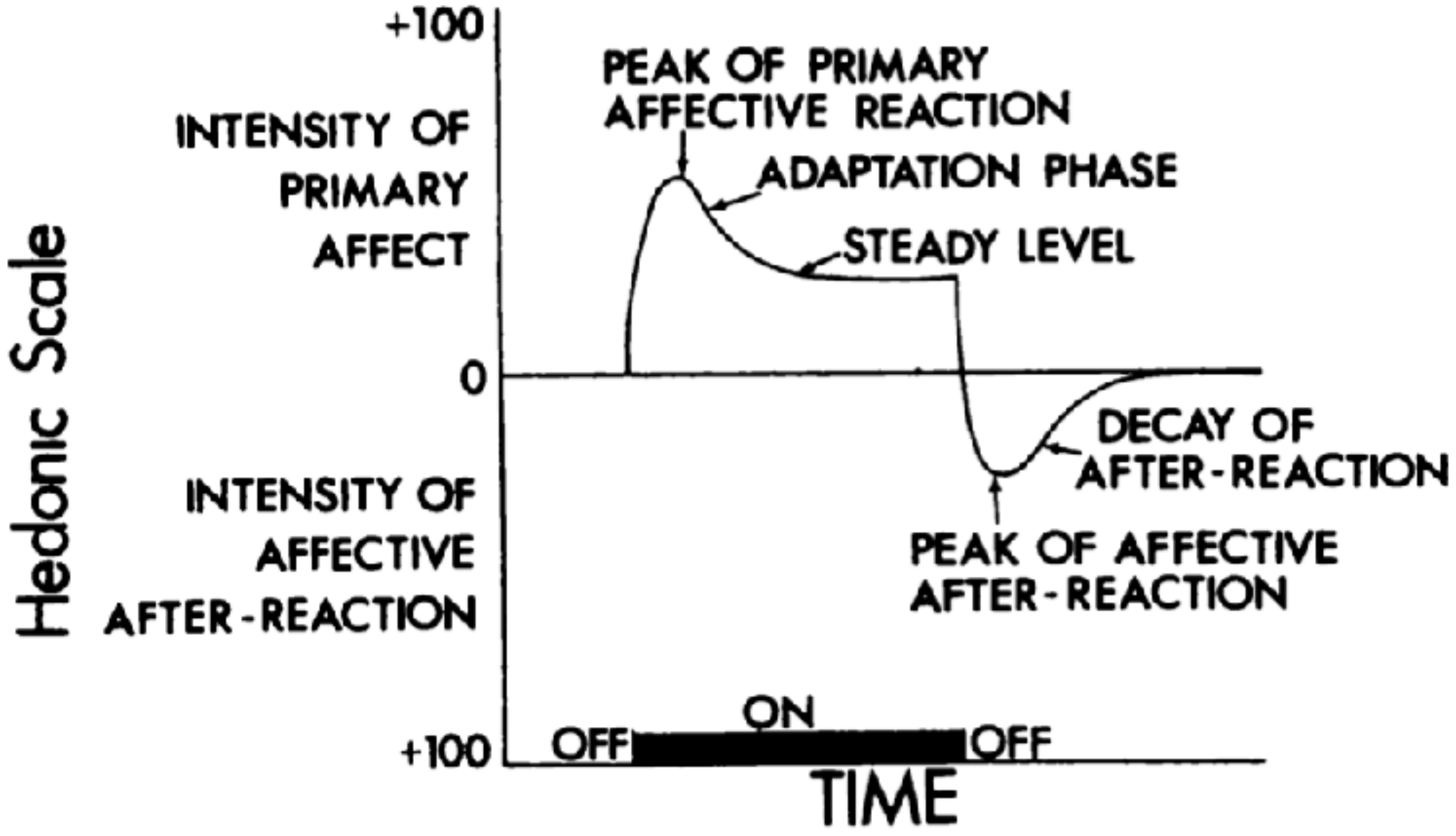
Tapering medication, drug cessation

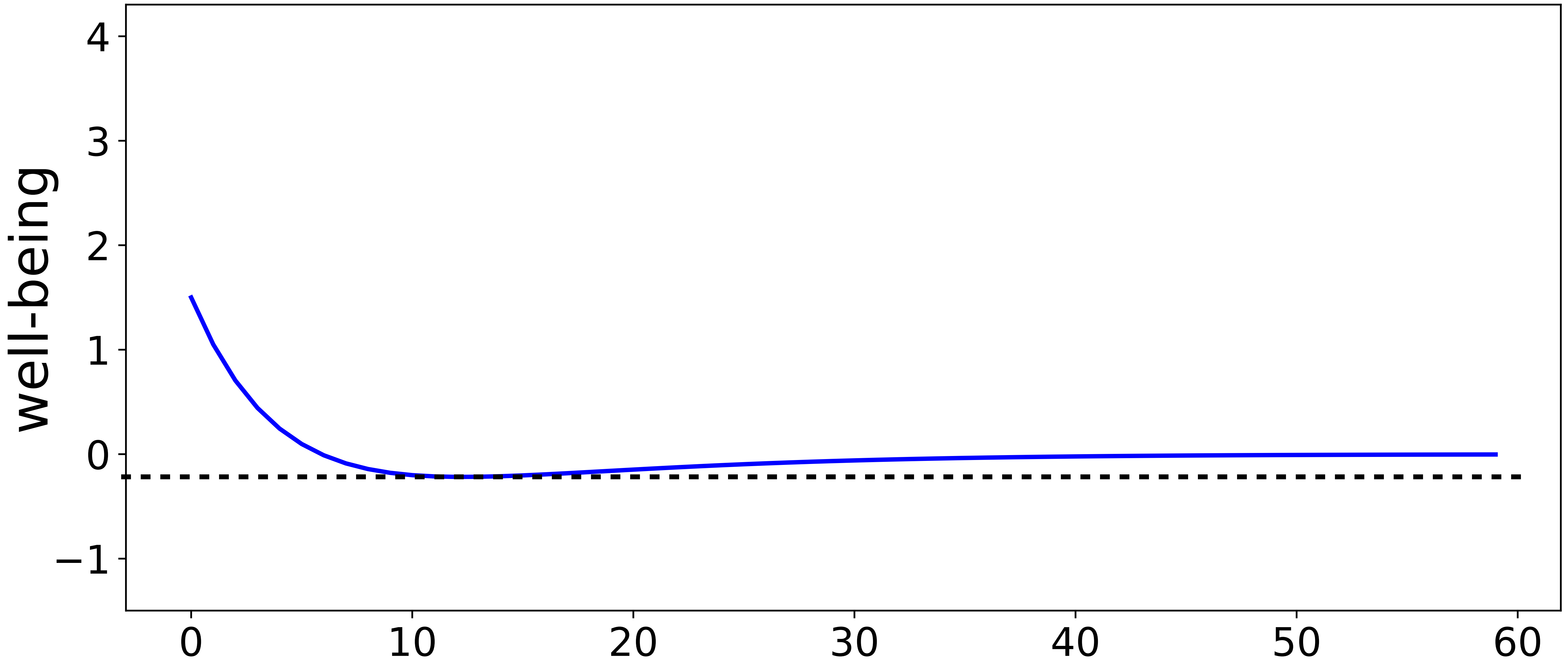
- Standard protocols for demedicating
- Linear or exponential decrease:
- Take 4/day this week, 3/day next week, 2/day the week after that…

- One-size fits all
- Widely reported negative consequences for tapering too rapidly.

Generalized Opponent Process Model

$$y_t = (g * u)_t + e_t$$





For some $\alpha > 0$

$g(t) > 0$	$t < t_0$	$g(t+1) \leq \alpha g(t)$	$t < t_0 - 1$
$g(t) \leq 0$	$t \geq t_0$	$\lvert g(t+1) \rvert \geq \alpha \lvert g(t) \rvert$	$t \geq t_0$

Generalized Opponent Process = -(Generalized Bannister IR)

A clairvoyant protocol needs no planning

$$\begin{array}{ll} \text{minimize} & \sum_{t=1}^{T} u_t \\ \text{subject to} & y_t \geq y_{\min} \\ & y_t = (g * u)_t \end{array}$$

Goal: Minimize the cumulative dose such that $y_t \geq y_{min}$ for all time.

Theorem [Gradu-R '23]: If the underlying system is an generalized opponent process, taking the dose at time t that results in $y_{t+1} = y_{min}$ yields the minimal cumulative dose.

A simple protocol for demedication

SES: subjective effect scale

EOD_SES = "how I felt yesterday"

SES_min = "the worst I can tolerate today"

dose[today] = dose[yesterday] - K (EOD_SES - SES_min)

K is in the range of 1 or 2.

Integral Control!

Theorem: If the underlying system is an opponent process, this protocol ensures

$$\frac{1}{T}\sum_{t=1}^{T} y_t \geq y_{\min} - \frac{y_0 - y_{\min}}{T}$$

Treatment maintenance

$$y_t = \sum_{k=0}^{t} g_k u_{t-k} + e_t = (g * u)_t + e_t$$

Sample goals:

Maximize Performance

$$\begin{array}{ll} \text{maximize} & y_T \\ \text{subject to} & y_t \geq y_{\min} \end{array}$$

Maximal final y, above some fixed level

Minimize Cumulative Dose

$$\begin{array}{ll} \text{minimize} & \sum_{t=1}^{T} u_t \\ \text{subject to} & y_t \geq y_{\min} \end{array}$$

Minimal *u* to keep *y* above a desired level

Plan treatment schedule

$$\begin{array}{ll} \text{minimize} & \sum_{t=1}^{T} u_t \\ \text{subject to} & y_T = y_{\text{end}} \end{array}$$

Choose *u* to to move *y* to a desired level

Minimize toxicity

$$\begin{array}{ll} \text{maximize} & \sum_{t=1}^{T} u_t \\ \text{subject to} & y_T \leq y_{\max} \end{array}$$

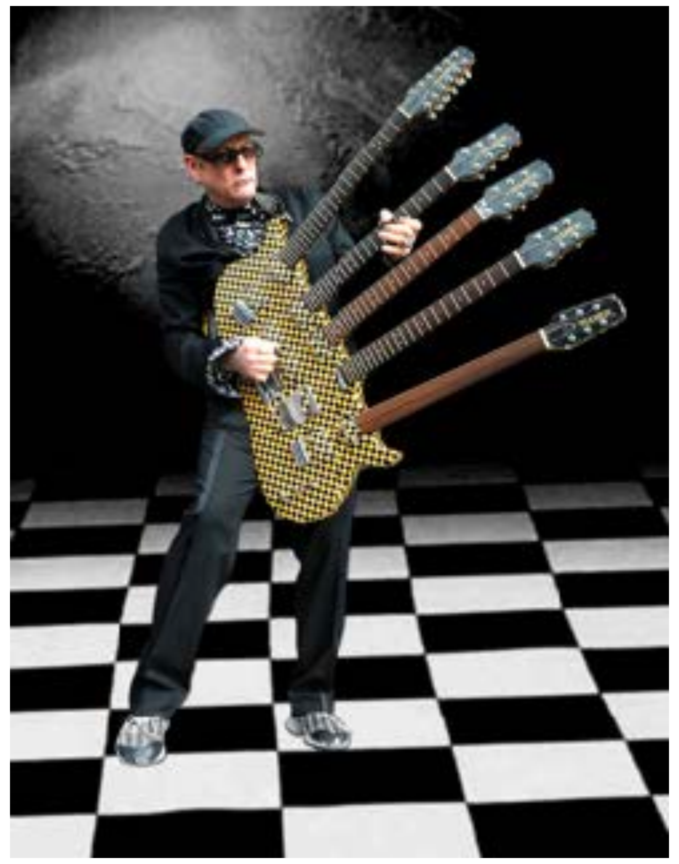
Apply as much *u*, keep *y* below a desired level

Towards Theory When N=1

- General qualitative theory of control of homeostatic systems.
- Don't need to know the model, why does this work with such coarse modeling?
- Better normative arguments and data driven derivations of opponent processes.
- Does knowing the math help? Customizing rest times? Other ways to derive better training?
- Coupled opponent processes and insights into periodization.
- What other dynamical systems can be trained with similar greedy heuristics? Perhaps more interestingly which cannot and what can be done in those settings?
- Collaborative training: sharing knowledge about different individuals to improve overall schemes. (This is what coaches/doctors/therapists do)
- Analyzing observational and interventional studies of individuals and generalizing from such studies to broader populations.

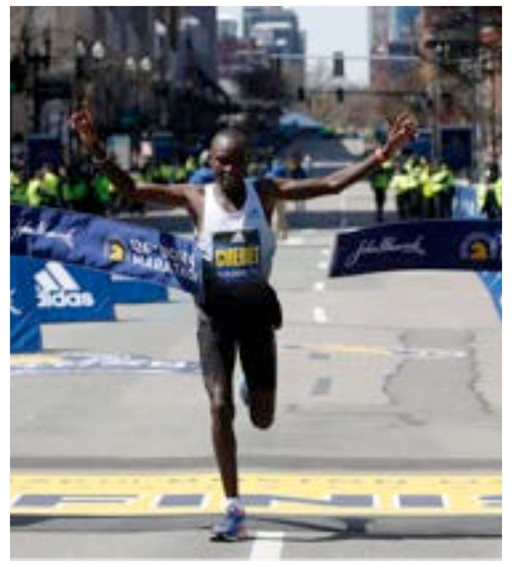
Learn a language

Manage mental health



Learn an instrument

Physical Therapy



Improve fitness

Treat a chronic condition

Dieting

How can you be the treatment and the control group?

Thanks!

- Special thanks to Murat Arcak, Dave Clarke, John Doyle, Paula Gradu, Mustafa Khammash, and Konrad Kording.

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