Dynamics of neuroendocrine stress response – the HPA axis and PTSD

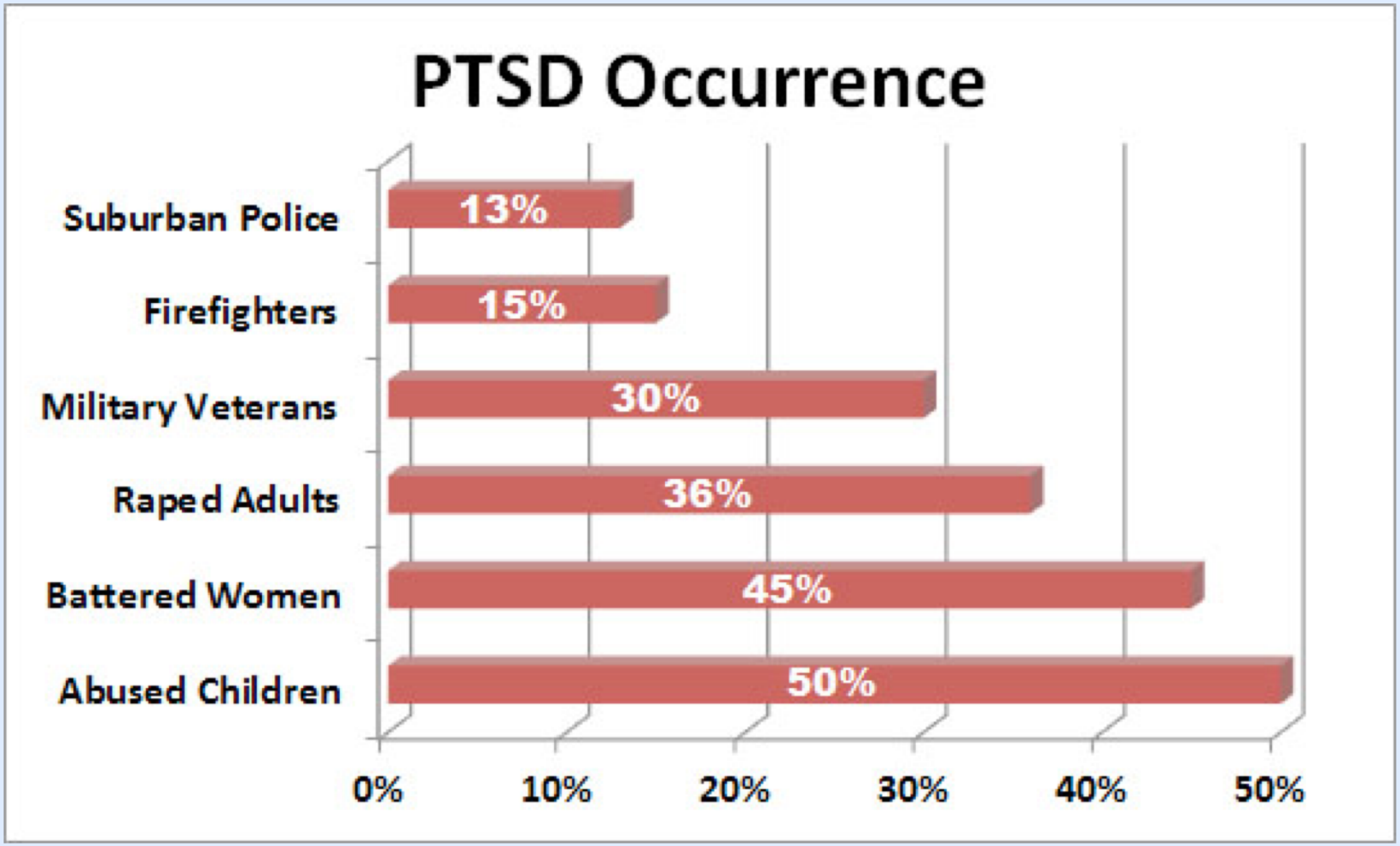
Maria R. D'Orsogna (CSUN), Tom Chou (UCLA), Lae Kim (UCLA), Apeshka Singh (UCLA)

PTSD: a mental health condition triggered by experiencing or seeing a terrifying event

Memories of trauma accompanied by intense emotional and physical reactions: flashbacks, nightmares, and anxiety, irritability, trembling, nausea, chronic pain

May last months or years

Three million new cases per year in the US



Death of a loved one, Car accidents, Natural disasters

Diagnosis of PTSD

Table 1 | **DSM-5 criteria for PTSD**

Criterion*	Description	Specific examples	Requirements	Compared with DSM-IV
Criterion A	Exposure to stressor	• Direct exposure • Witnessing trauma • Learning of a trauma • Repeat or extreme indirect exposure to aversive details	DSM-5 recognizes that exposure to trauma can occur either by direct or indirect confrontation with extreme trauma	Specific definition of details of the stressor needed, including repeated experience or extreme exposure to details of events
Criterion B	Intrusion symptoms	• Recurrent memories • Traumatic nightmares • Dissociative reactions (flashbacks) • Psychological distress at traumatic reminders • Marked physiological reactivity to reminders	At least one of these five examples is required	No change, but further clarification of the dissociative quality of flashbacks needed
Criterion C	Persistent avoidance	• Trauma-related thoughts or feelings • Trauma-related external reminders such as people, places or activities	At least one of these two examples is required	DSM-IV did not separate the avoidance criterion
Criterion D	Negative alterations in cognitions and mood	• Dissociative amnesia • Persistent negative beliefs and expectations • Persistent distorted blame of self or others for causing trauma • Negative trauma-related emotions: fear, horror, guilt, shame and anger • Diminished interest in activities • Detachment or estrangement from others • Inability to experience positive emotions	At least two of these seven examples are required	DSM-IV noted social estrangement and restricted the range of affect; numbing redefined to positive rather than all affects
Criterion E	Alterations in arousal and reactivity	• Irritable and aggressive behaviour • Self-destructive and reckless behaviour • Hypervigilance • Exaggerated startle • Problems concentrating • Sleep disturbance	At least two of these six examples are required	Self-destructive and risk-taking behaviours were not defined in DSM-IV

Diagnostic and Statistical Manual of Mental Health Disorders – 5 APA

Treatment

Table 4 | **Key recommendations from several clinical practice guidelines for PTSD**

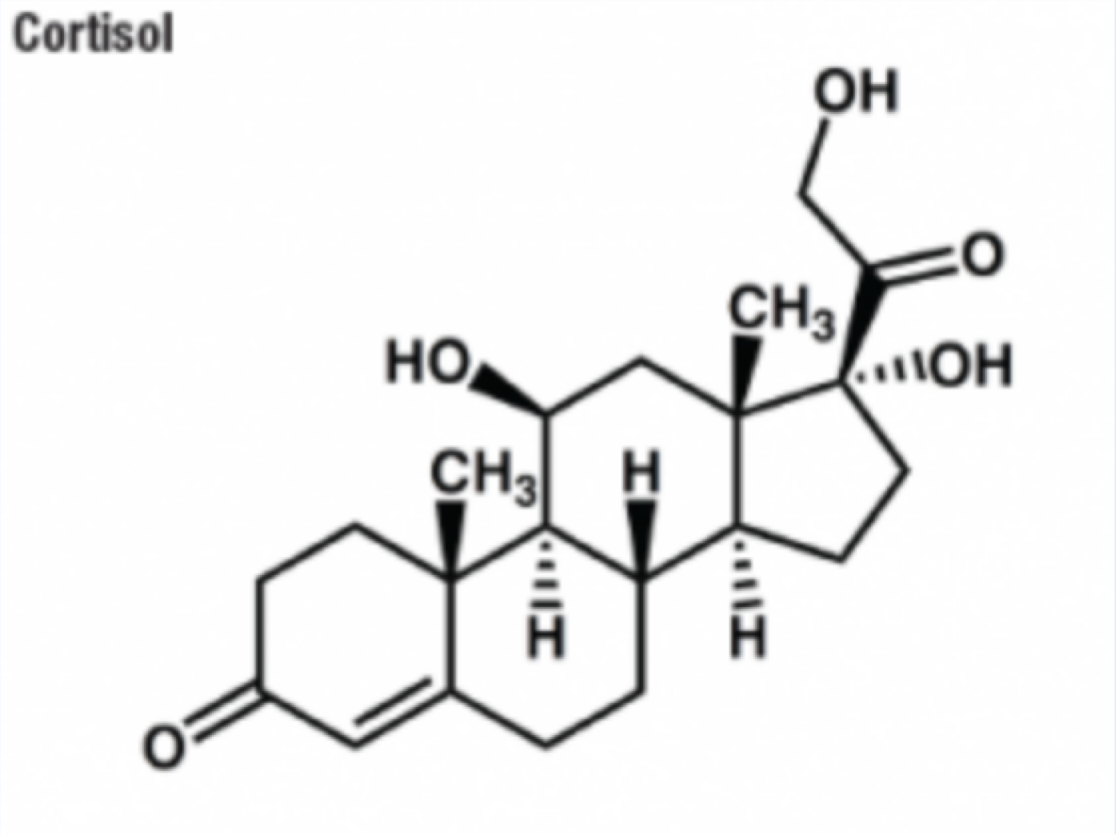
Guideline	Year	Recommendations	Refs
UK National Institute for Health and Care Excellence	2005	Trauma-focused cognitive behavioural therapy or EMDR recommended as first-line treatment. Drug treatments should not be used as a routine first-line treatment	246
Canadian Psychiatric Association		treatments. Mirtazapine, fluvoxamine, phenelzine, moclobemide, with or without adjuctive olanzapine or risperidone recommended as second-line treatments.	
International Psychopharmacology Algorithm Project	2005–2011	Prazosin and trazodone are emphasized at initial step; if considerable PTSD symptoms remain, an antidepressant (SSRI, SNRI or TCA) may be tried. With partial improvement and residual symptomatology, augmentation may be tried; the best options are antipsychotics, clonidine, topiramate and lamotrigine.	248
International Society for Traumatic Stress Studies	2005–2009	Cognitive behavioural therapy that comprises exposure therapy, cognitive therapy, stress inoculation training or a combination of these; or EMDR; or SSRIs; or SNRIs are all	249,250
American Psychiatric Association	2004 and 2009	Cognitive behavioural therapy, SSRIs or EMDR are all considered to have strong evidence of efficacy. Various other medications may be useful.	251,252
US Veterans Affairs and Department of Defense	2	psychotherapy that includes components of exposure treatments. Other medications may be useful.	
Australian Centre Posttraumat	2013	Trauma-focused cognitive behavioural interventions or EMDR with *in vivo* exposure are	254

EMDR, eye movement desensitization and reprocessing; PTSD, post-traumatic stress disorder; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

EMDR - Eye Movement Desensitization and Reprocessing

Biological markers?

Major player in PTSD: cortisol



Major player in PTSD: cortisol

Cortisol: a steroid hormone (glucocorticoid)

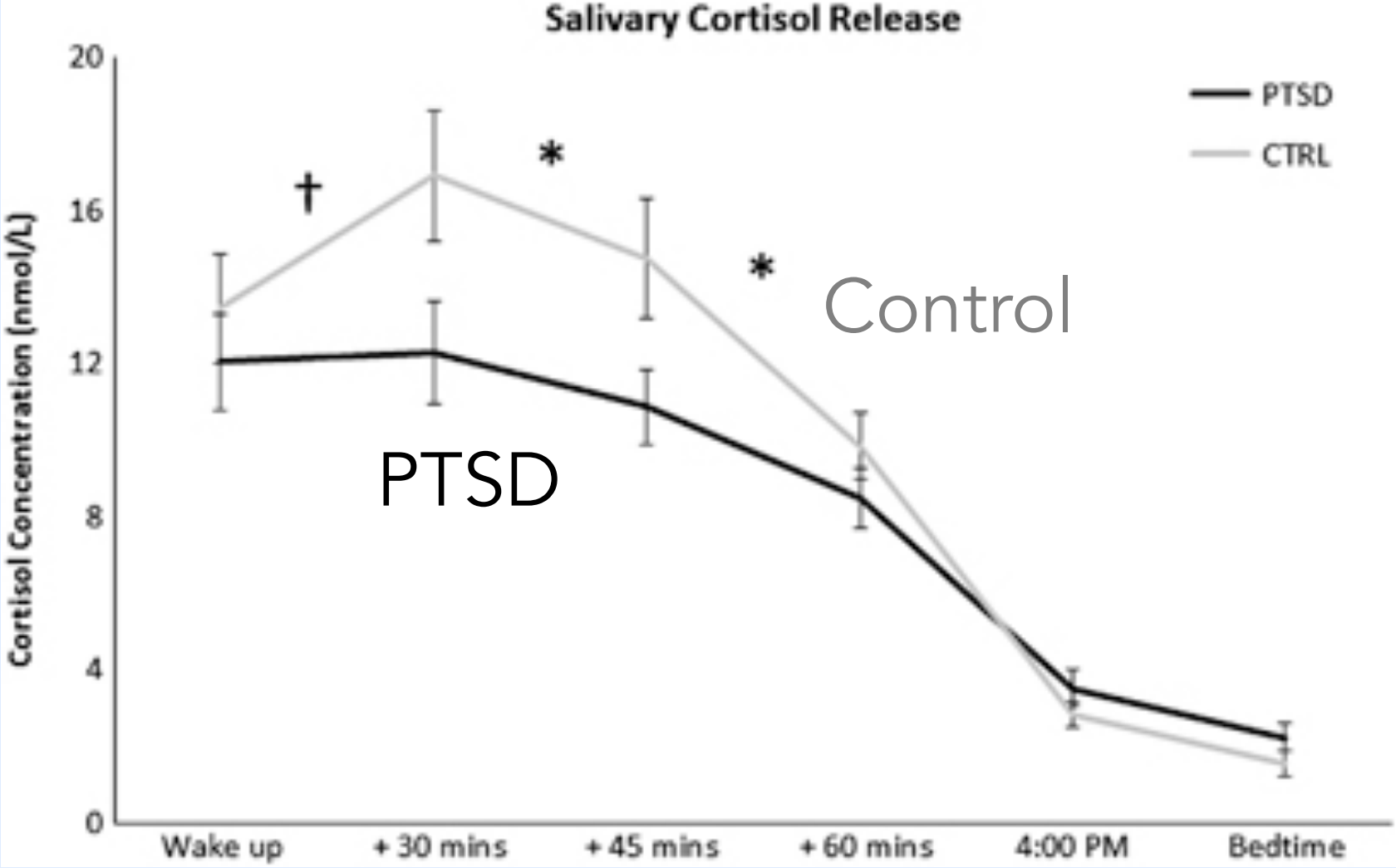
Released in response to stress and low blood glucose concentrations

Facilitates fear extinction, increases blood sugar, suppresses the immune system, wound healing, regulates metabolism, influences memory

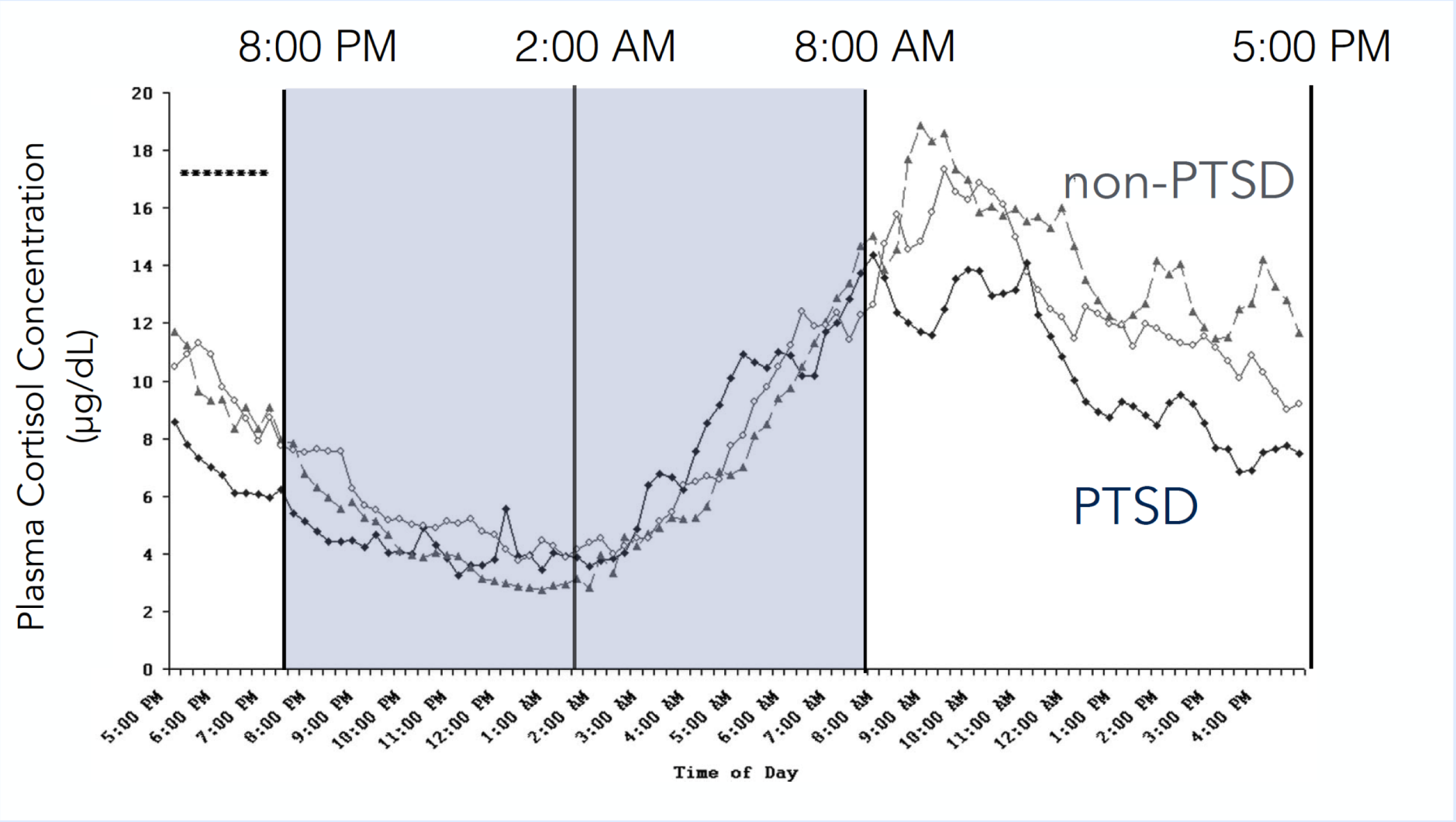
Hypo vs. hypercortisolism

Basal (un-stimulated) cortisol:
LOWER in PTSD patients

Cortisol


Salivary Cortisol Release
Cortisol Concentration (nmol/L)
20
16
12
8
4
0
PTSD
CTRL
†
*
*
Control
PTSD
Wake up
+ 30 mins
+ 45 mins
+ 60 mins
4:00 PM
Bedtime

Cortisol

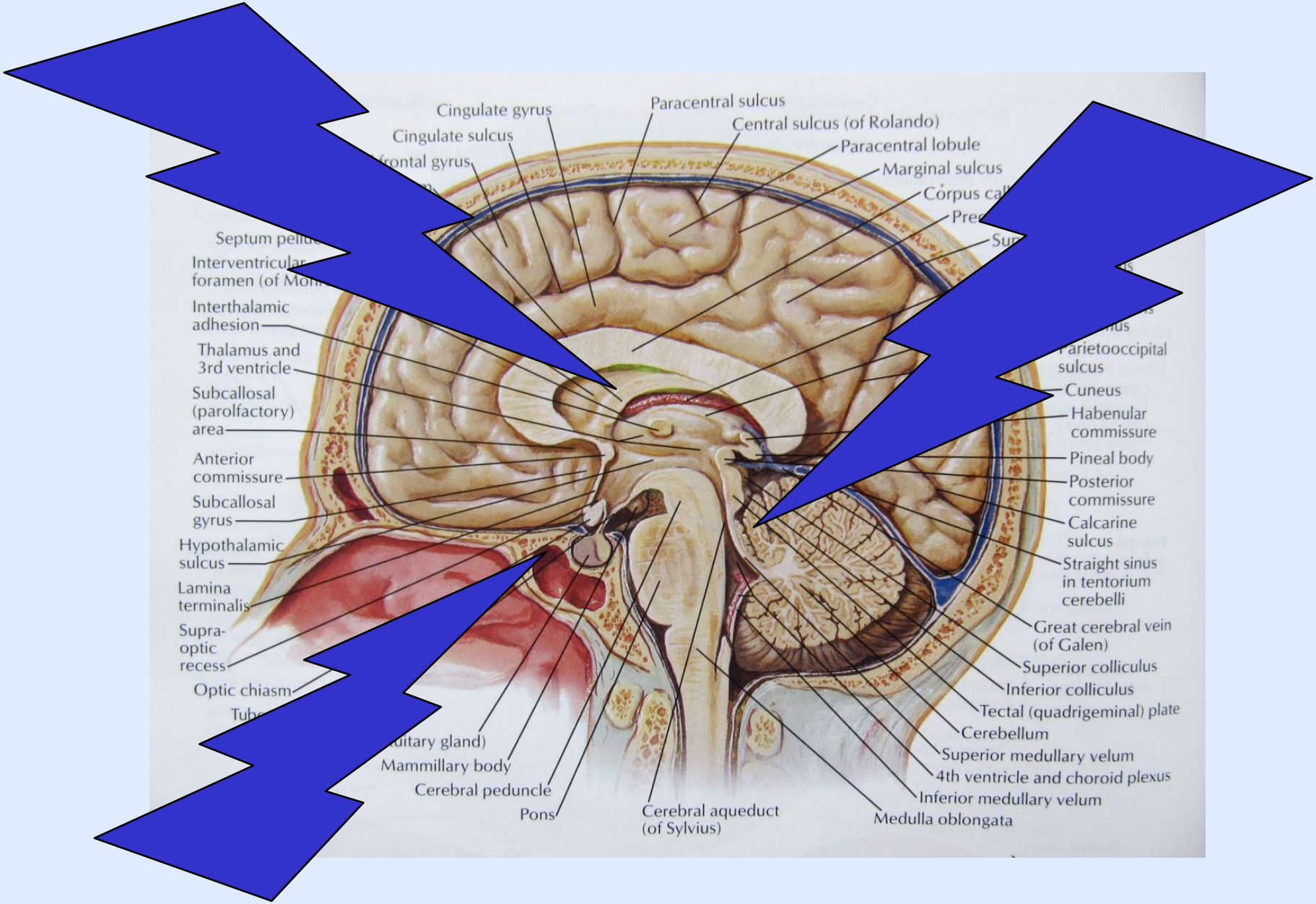


Cortisol oscillates with hourly and diurnal cycles

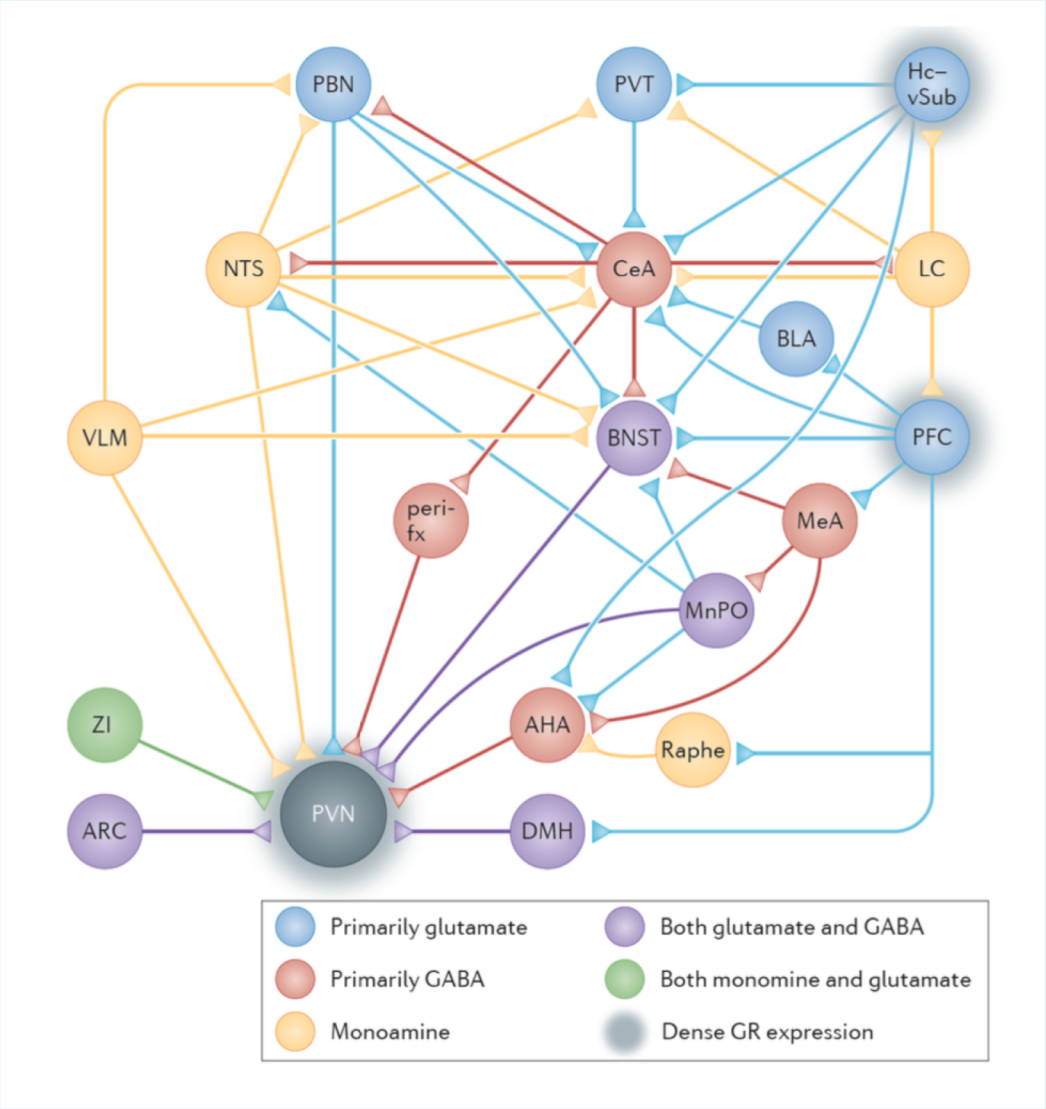
How does trauma – stress lead to lower cortisol in PTSD patients?

How does this happen without physical injury (TBI)?

Stress and the brain

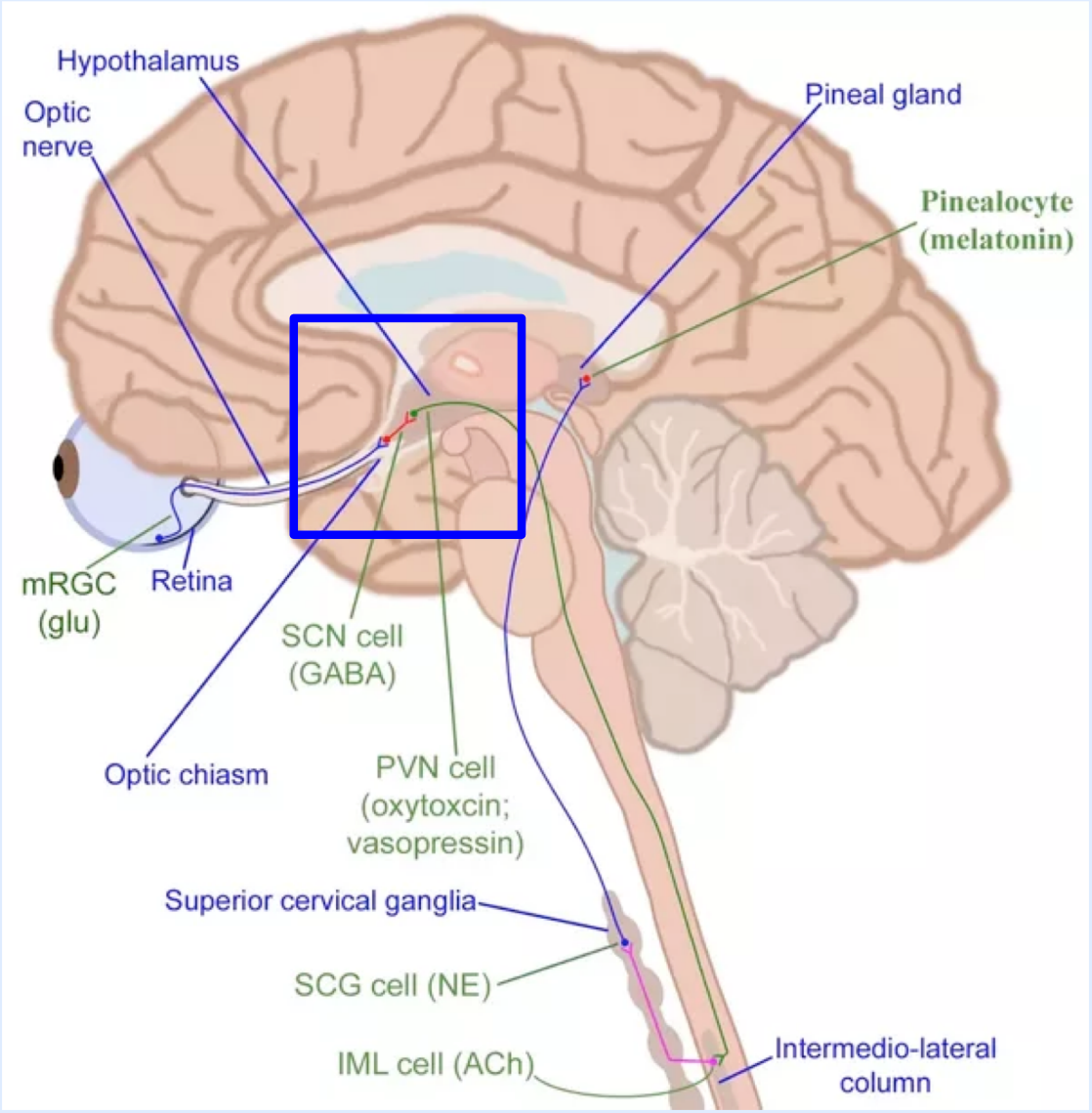


Stress and the brain



Input to the PVN in the hypothalamus

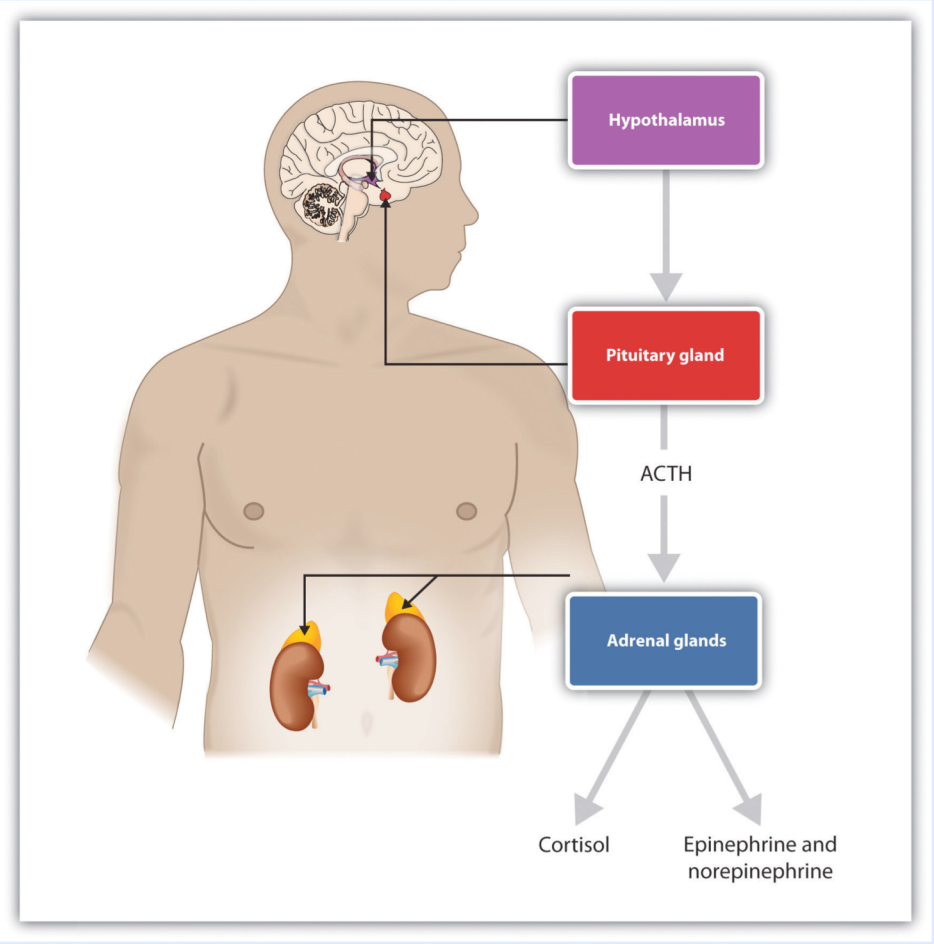
Stress and the brain



Input to the PVN in the hypothalamus

The HPA axis

Hypothalamus Pituitary Adrenal Axis

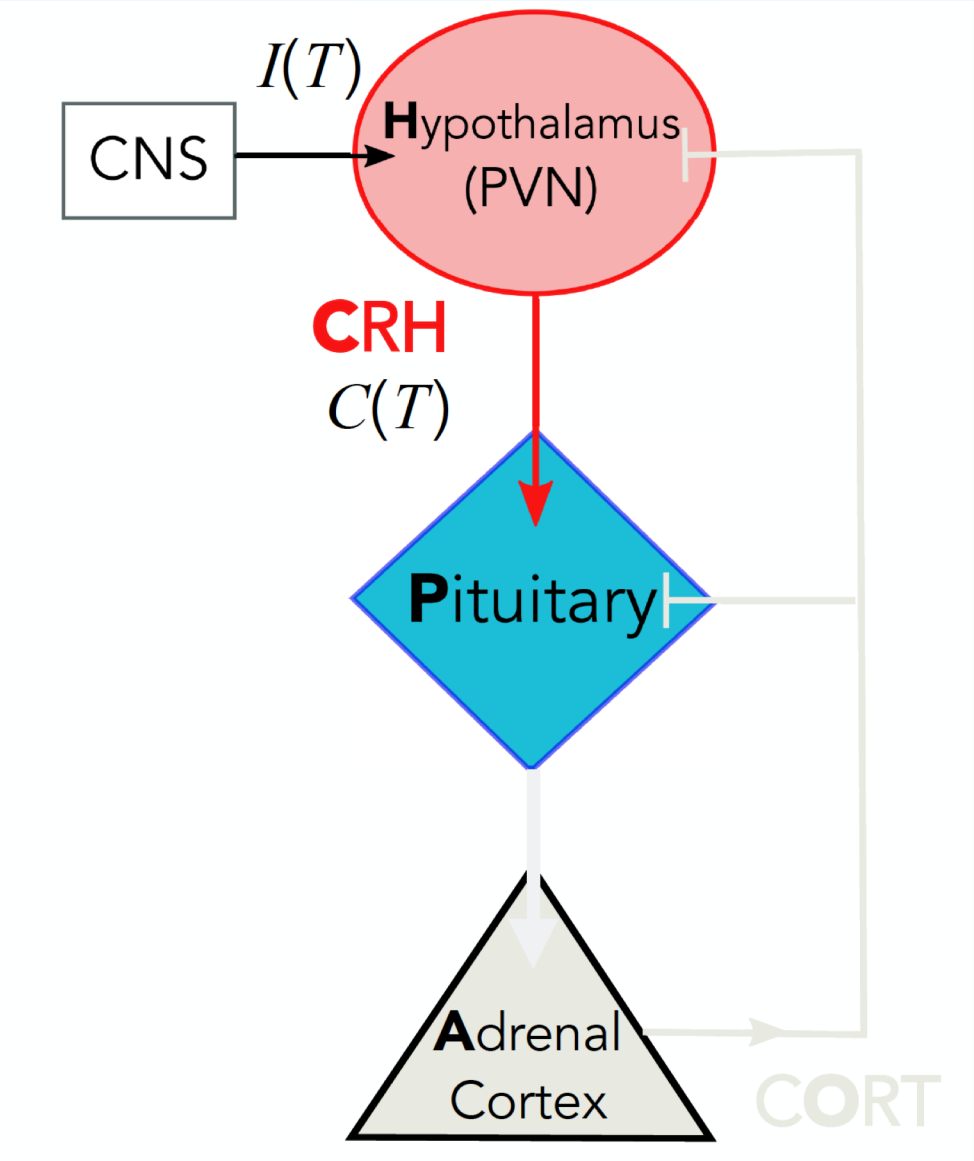


Hypothalamus (PVN)
(nervous system control)

Pituitary & Adrenal
(hormonal glands)

HPA axis

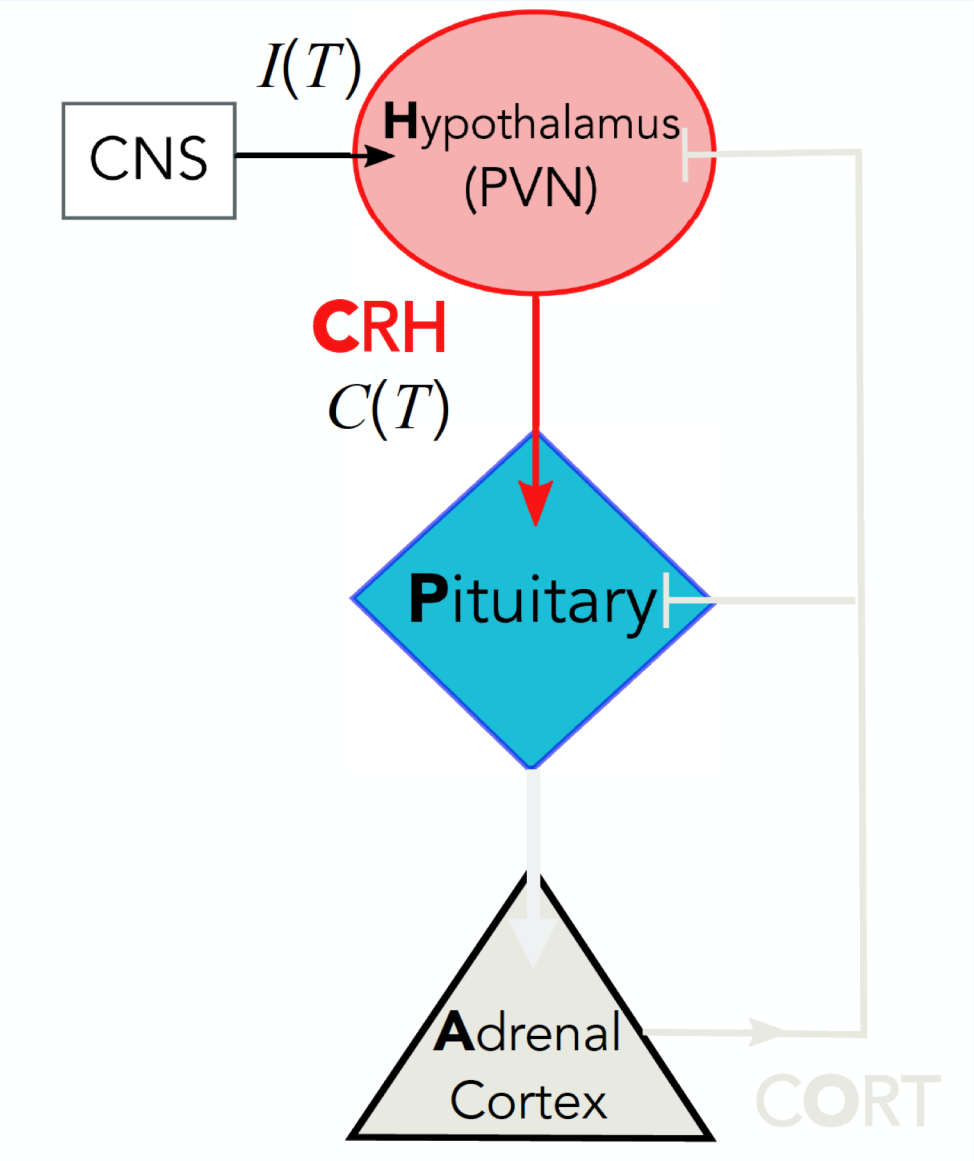
The HPA axis



I(t) = input
(basal and/or external)

Central Nervous System sends a "signal" to the PVN in the hypothalamus

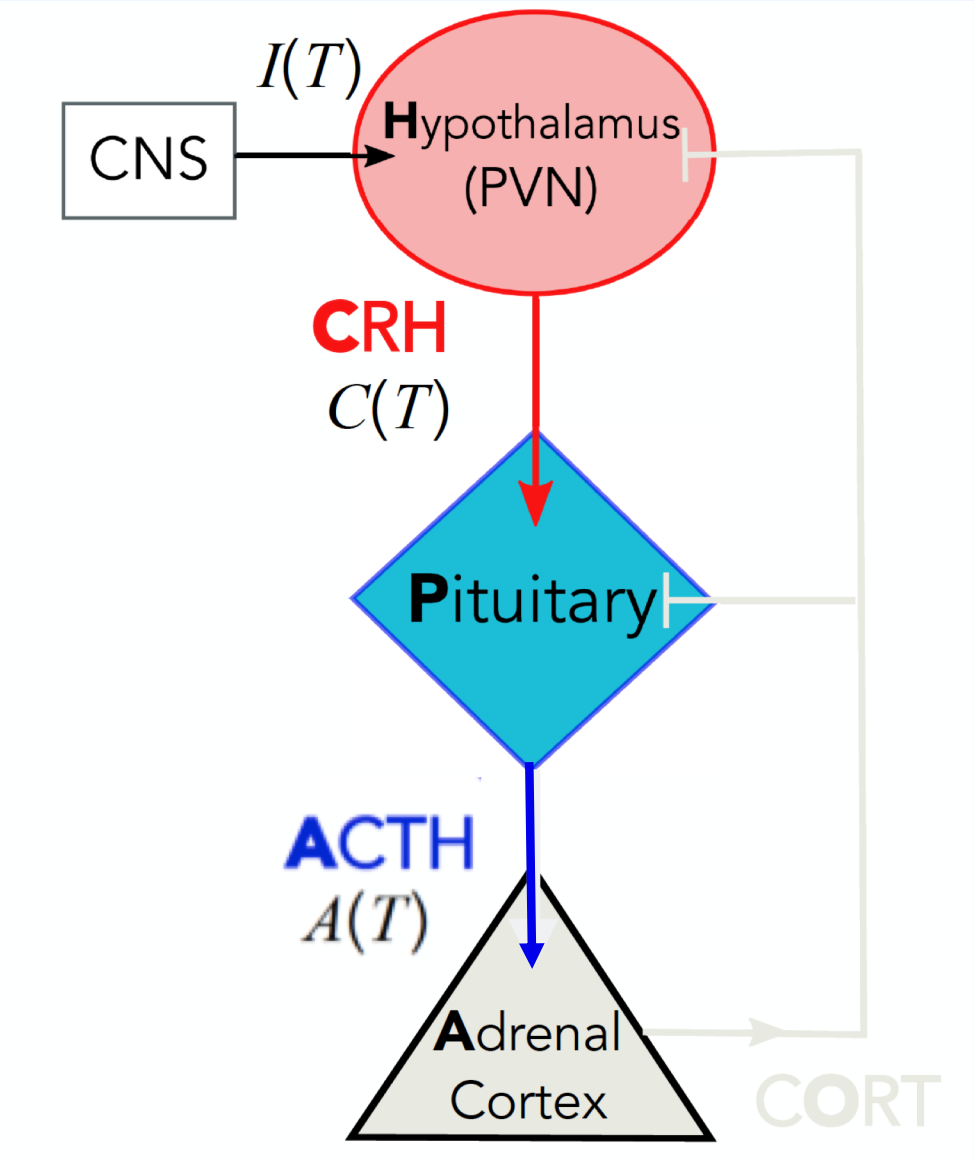
The HPA axis



The PVN in the Hypothalamus releases CRH into the hypo-physeal portal vein to the pituitary gland

CRH = corticotropin releasing hormone

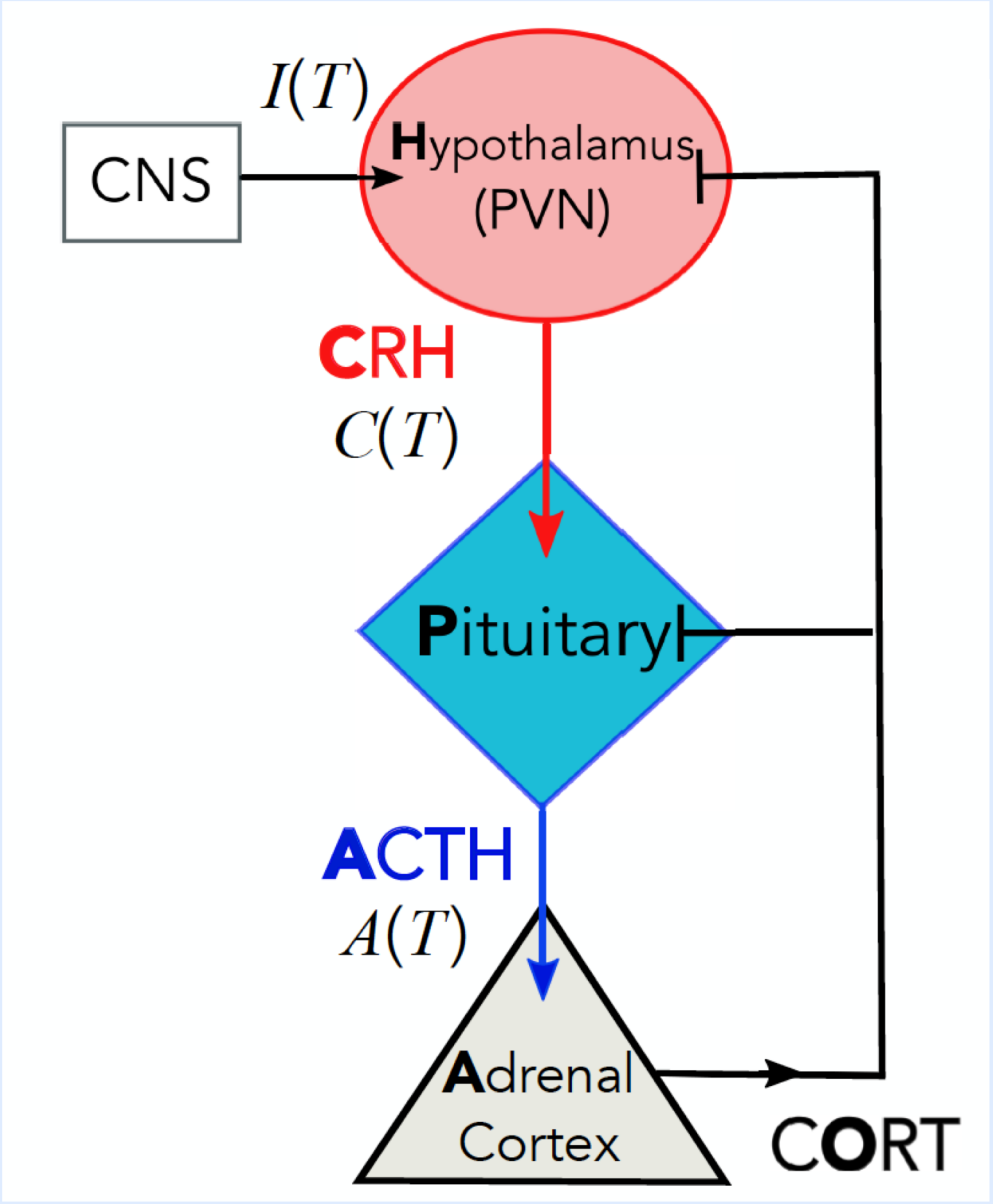
The HPA axis



The pituitary gland releases ACTH into the bloodstream

ACTH = adreno-corticotropin hormone

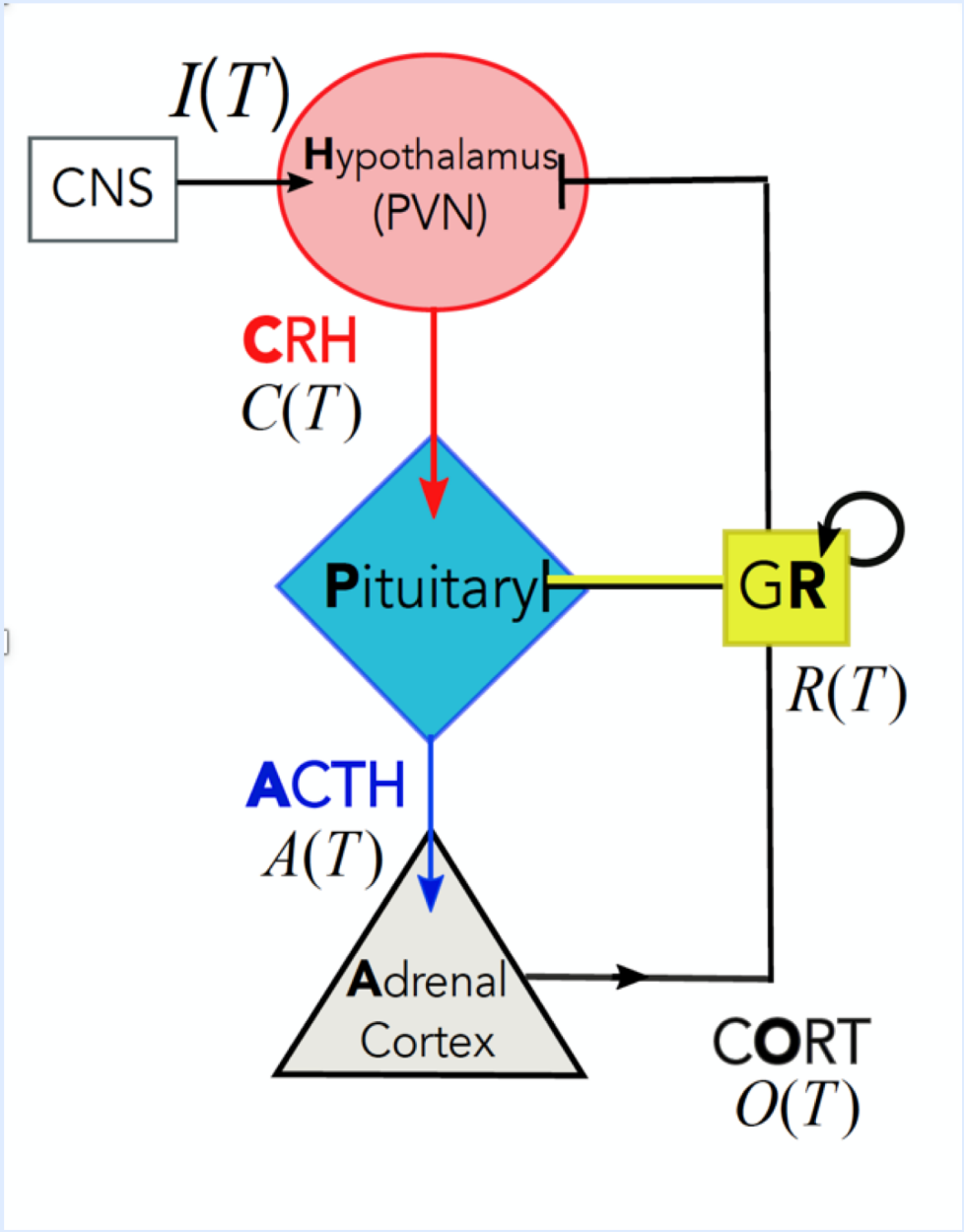
The HPA axis



The adrenal cortex synthesizes and secretes CORT into the bloodstream

CORT = cortisol hormone

The HPA axis



Cortisol imparts a negative feedback on the pituitary and on the hypothalamus

Cortisol binds to the glucocorticoid receptor GR, and stimulates further GR production in the pituitary through homodimerization

CORT = cortisol hormone

GR Homodimerization

Mol Endocrinol. 1992 Aug;6(8):1299-309.

Homodimer formation is rate-limiting for high affinity DNA binding by glucocorticoid receptor.

Drouin J[1], Sun YL, Tremblay S, Lavender P, Schmidt TJ, de Léan A, Nemer M.

Author information

Abstract

The glucocorticoid receptor (GR) is a hormone-inducible transcription factor which activates transcription of specific genes by binding to a DNA sequence present in the promoters of inducible genes. These glucocorticoid response elements (GREs) have a conserved palindromic sequence. Each half-GRE palindrome binds one subunit of GR. We have assess
formation is
approximate
were very st
preferentiall
GRE bindin
(largely hom
rate-limiting
to bind GR
work, these
transcription

Cell. 1988 Oct 21;55(2):361-9.

Molecular interactions of steroid hormone receptor with its enhancer element: evidence for receptor dimer formation.

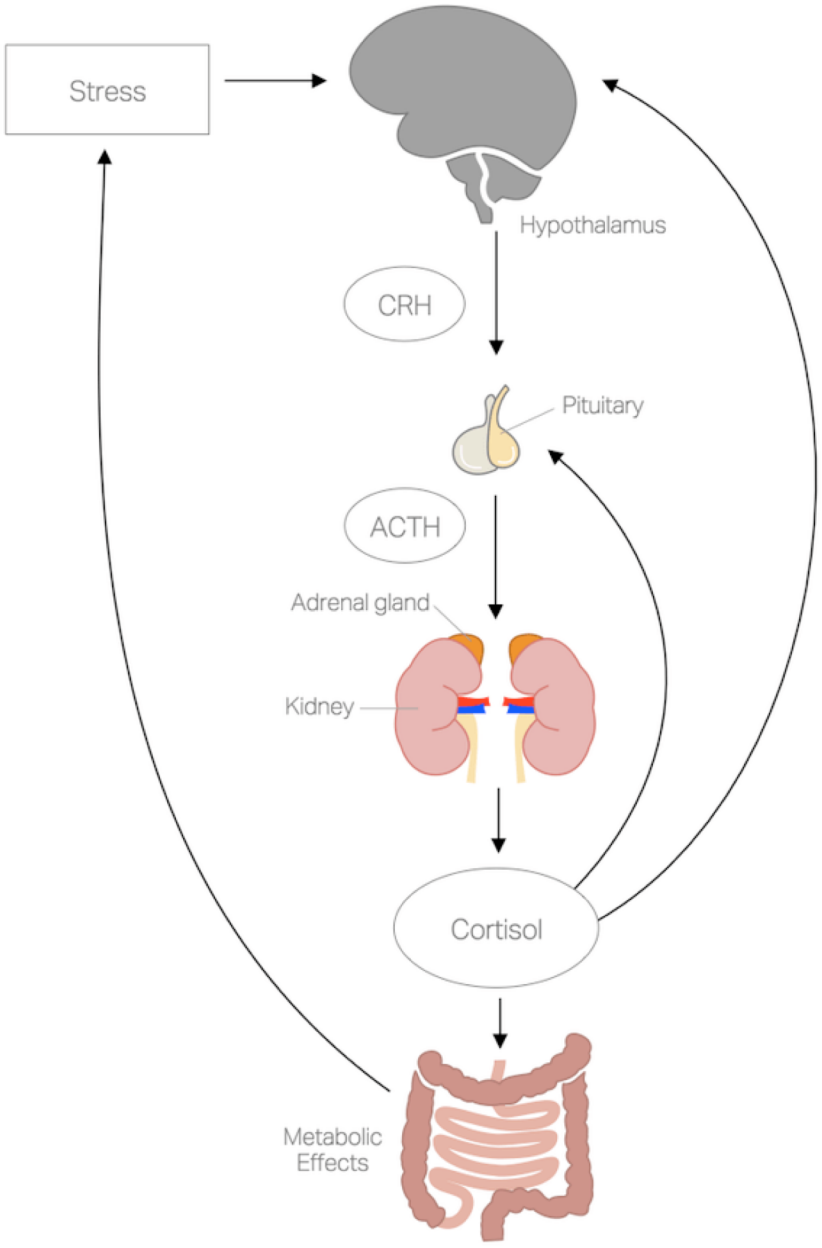
Tsai SY[1], Carlstedt-Duke J, Weigel NL, Dahlman K, Gustafsson JA, Tsai MJ, O'Malley BW.

Author information

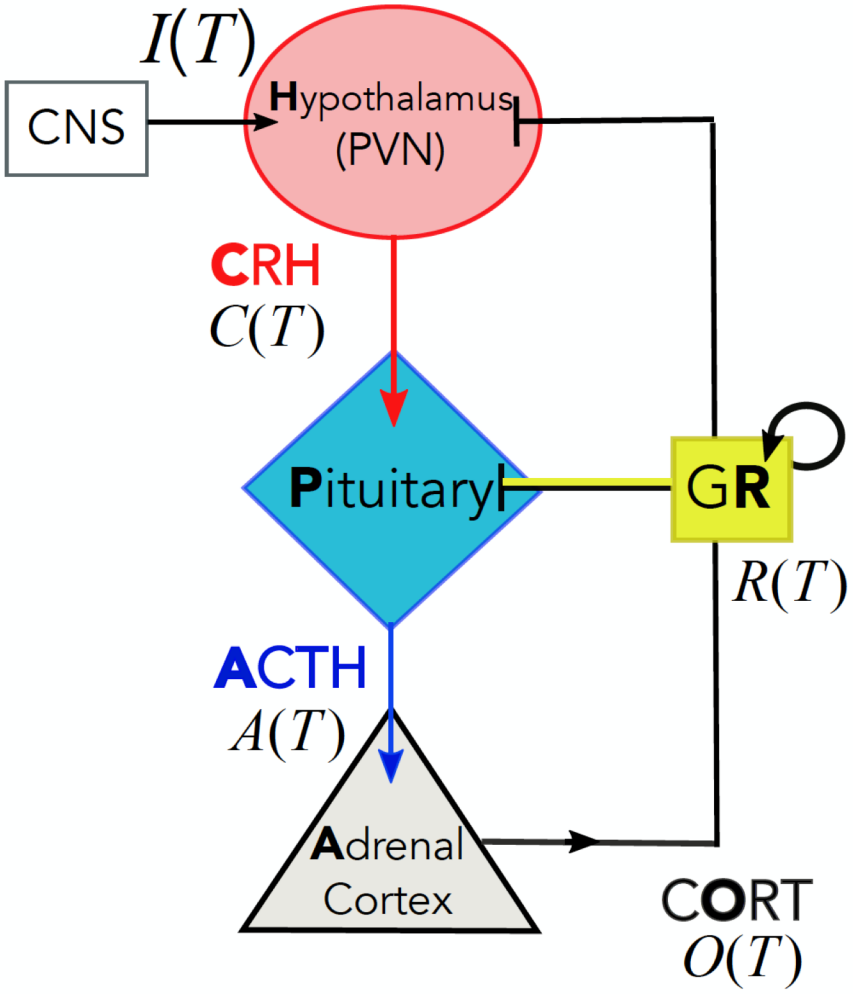
Abstract

A steroid hormone responsive element (GRE/PRE), sufficient to confer glucocorticoid and progesterone inducibility when linked to a reporter gene, was used in band-shift assays to examine its molecular interactions with steroid hormone receptors. Both progesterone and glucocorticoid receptors bound directly and specifically to the GRE/PRE. The purine contact sites for both form A and form B chicken progesterone receptor, as well as those for rat glucocorticoid receptor, are identical. A peptide fragment produced in bacteria that primarily contain the DNA binding domain of the glucocorticoid receptor binds first to the TGTTCT half-site of the GRE/PRE, and a second molecule binds subsequently to the TGTACA (half-site) of the GRE/PRE in a cooperative manner. Utilizing the peptide fragment and the protein A-linked fragment, we demonstrated that the receptor interacts with its cognate enhancer as a dimer.

HPA Axis


Stress
Hypothalamus
CRH
Pituitary
ACTH
Adrenal gland
Kidney
Cortisol
Metabolic
Effects

How can we model the HPA axis?



- State variables:

C : **C**RH concentration

A : **A**CTH concentration

O : C**O**RT concentration

R : G**R** (cortisol-receptor) conc.

What do we want from this model?

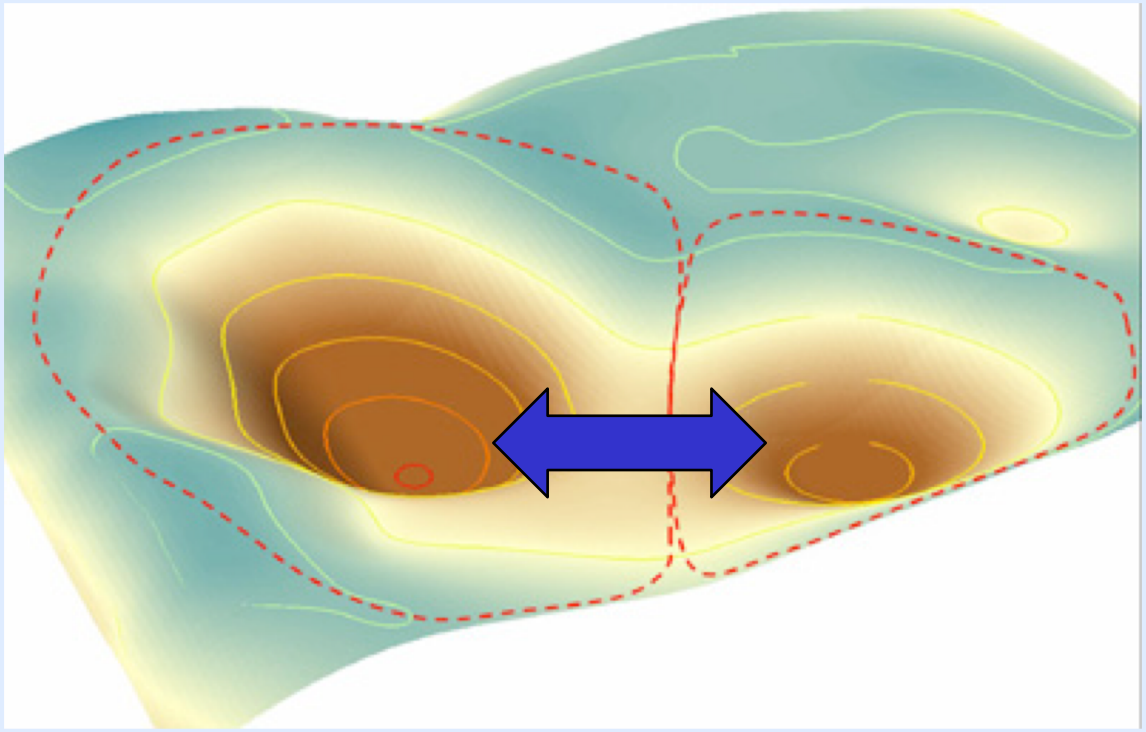
1. Steady states with “low” cortisol (diseased state) and “high” cortisol (normal state)

“hypocortisolism”

What do we want from this model?

1. Steady states with “low” cortisol (diseased state) and “high” cortisol (normal state)

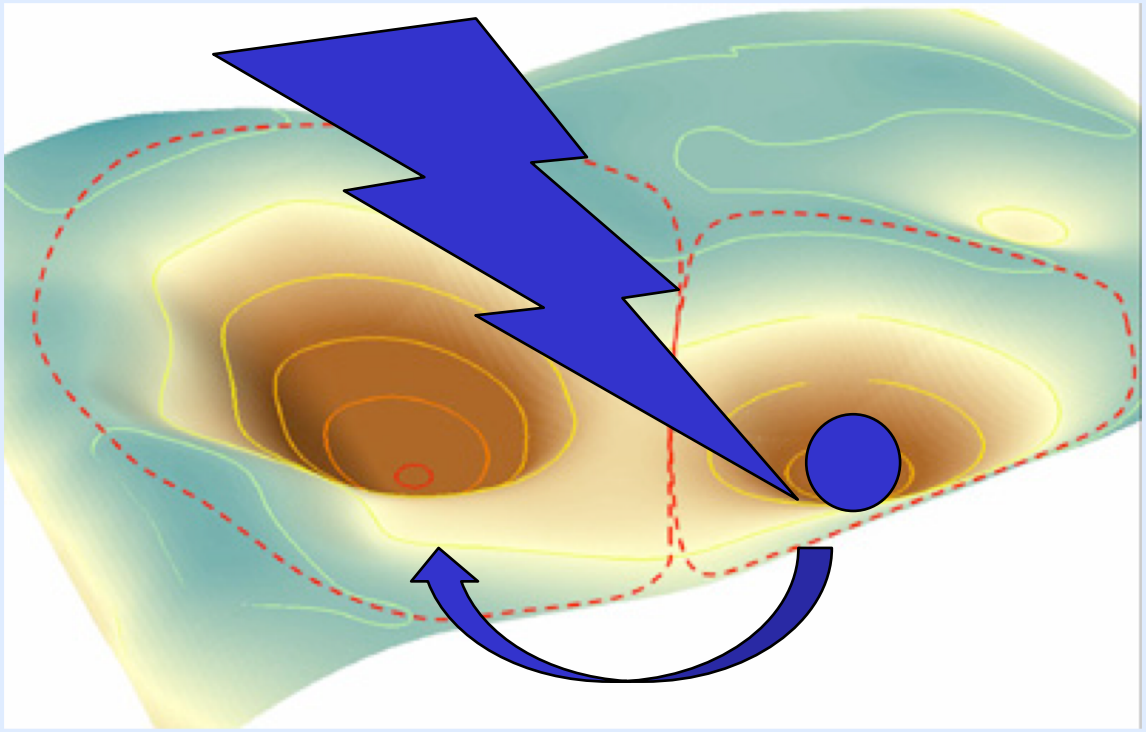
Bistability -- hypocortisolism



Bistability:

May explain how PTSD arises without physical trauma

We don't need changes in parameters (physical trauma)
just external input (psychological trauma)



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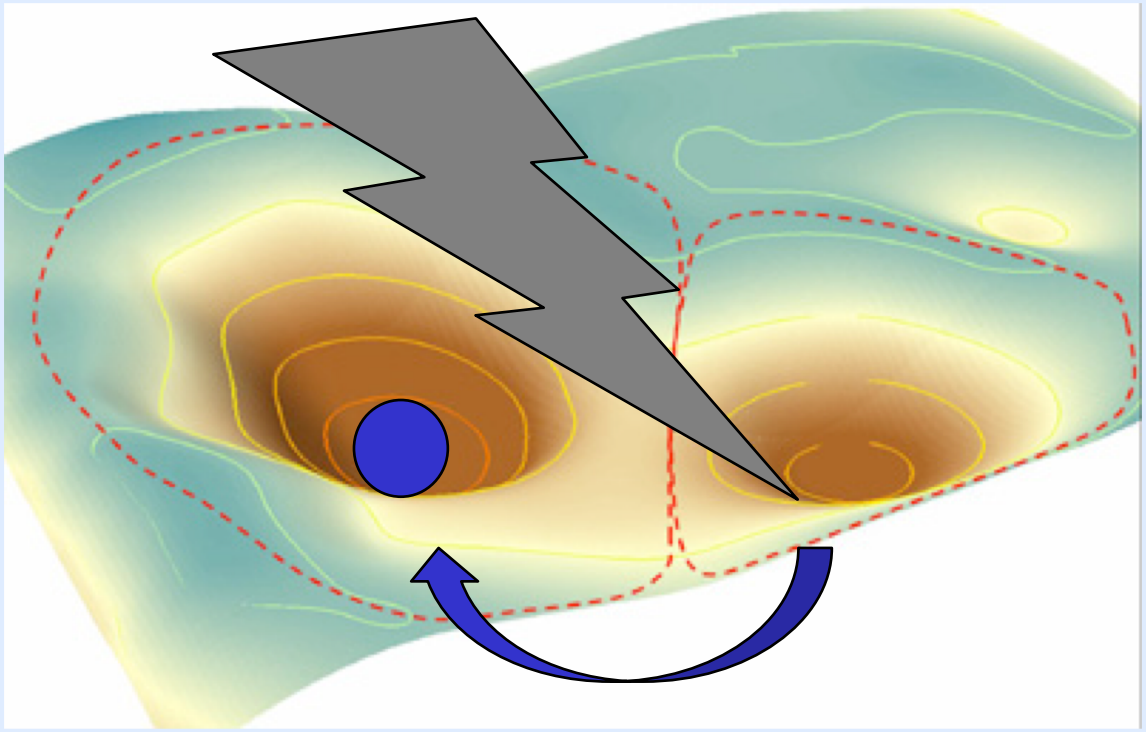


What do we want from this model?

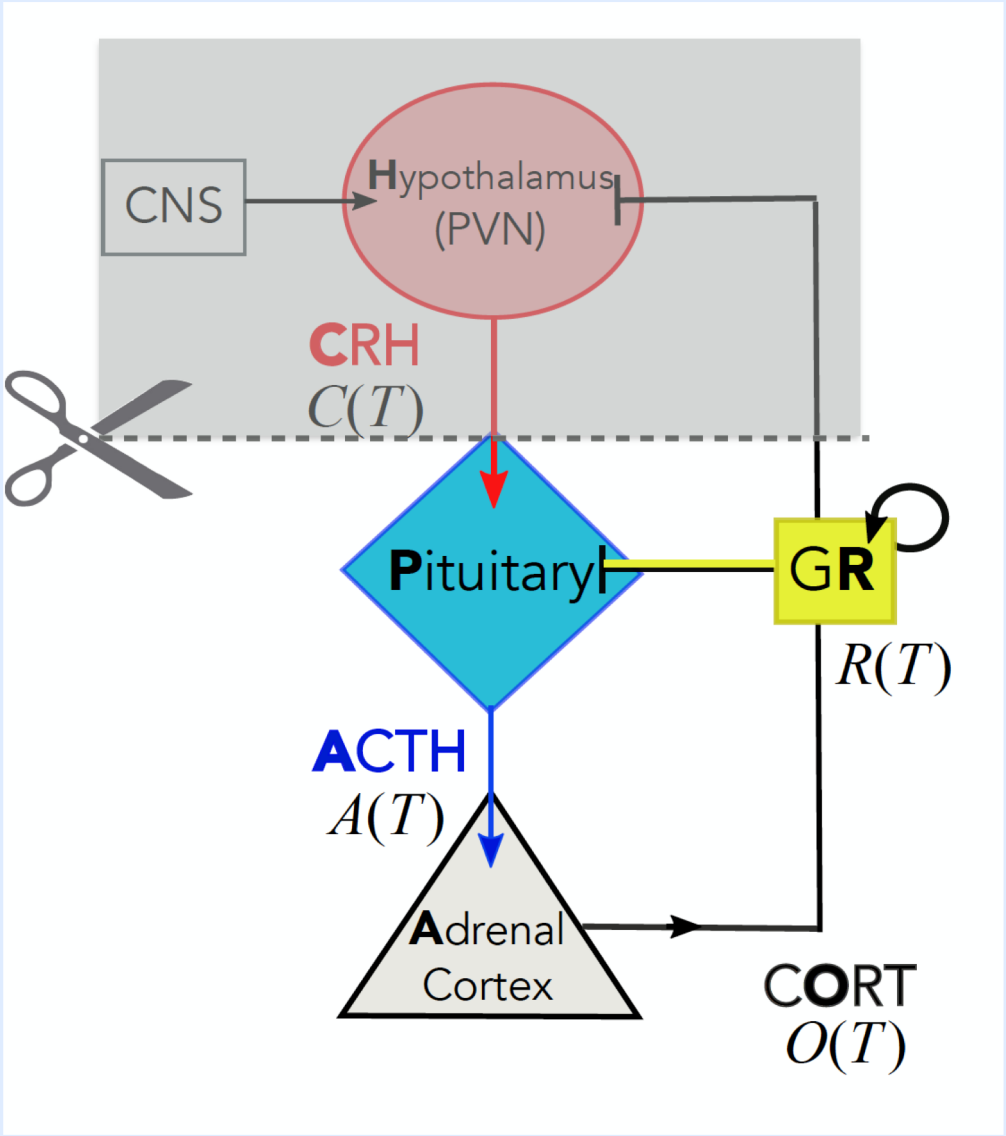
1. Steady states with “low” cortisol (diseased state) and “high” cortisol (normal state)

“hypocortisolism”

2. Reproduce realistic features such as oscillations in cortisol (and ACTH – no oscillations in CRH)

So let’s build our model

From experiments on sheep:



Oscillations in CORT and ACTH persist even after surgically removing the hypothalamus

The PA system (without H) should still support oscillations

From experiments on sheep:

Endocrinology. 1990 Oct;127(4):1956-66.

Studies of the regulation of the hypothalamic-pituitary-adrenal axis in sheep with hypothalamic-pituitary disconnection. II. Evidence for in vivo ultradian hypersecretion of proopiomelanocortin peptides by the isolated anterior and intermediate pituitary.

Engler D[1], Pham T, Liu JP, Fullerton MJ, Clarke IJ, Funder JW.

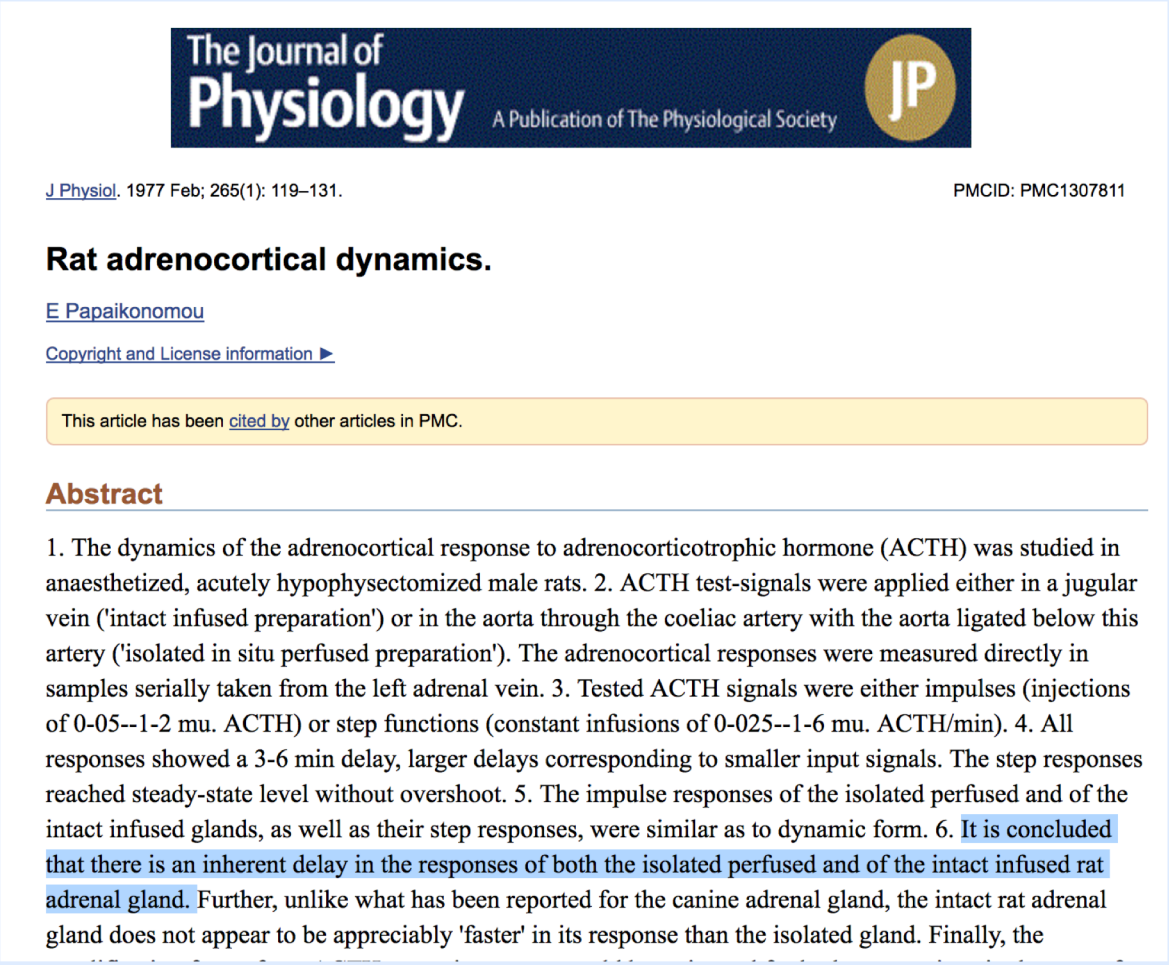
Author information

Abstract

Studies were performed to determine whether the isolated ovine anterior and intermediate pituitary might rhythmically secrete three POMC peptides, ACTH, ir-beta-endorphin (ir-beta-EP), and ir-alpha-melanocyte stimulating hormone (ir-alpha-MSH) in vivo. When blood was taken at 10-min intervals from four ewes with hypothalamo-pituitary-disconnection (HPD), a distinct POMC-peptide and cortisol ultradian rhythm was noted. A comparison of the four HPD ewes with five nonstressed hypothalamopituitary-intact (HPI) ewes revealed that the mean plasma levels of the three POMC-peptides and cortisol were increased, the mean ACTH and ir-alpha-MSH pulse amplitudes were increased, and the mean ir-beta-EP and ir-alpha-MSH interpulse intervals were decreased. When four HPI ewes were subjected to a mild stress, plasma POMC-peptide and cortisol levels increased significantly when compared with the five unstressed HPI animals. In addition,

D Engler, Endocrinology (1990)

From experiments on rats:



The Journal of Physiology
A Publication of The Physiological Society

J Physiol. 1977 Feb; 265(1): 119–131. PMCID: PMC1307811

Rat adrenocortical dynamics.

E Papaikonomou

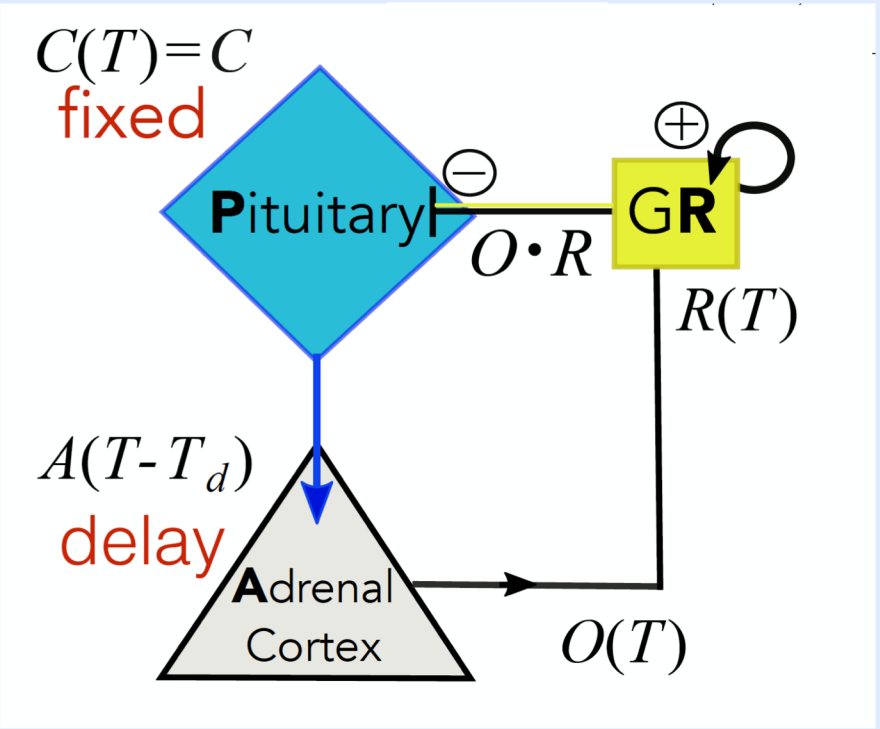
Abstract

1. The dynamics of the adrenocortical response to adrenocorticotrophic hormone (ACTH) was studied in anaesthetized, acutely hypophysectomized male rats. 2. ACTH test-signals were applied either in a jugular vein ('intact infused preparation') or in the aorta through the coeliac artery with the aorta ligated below this artery ('isolated in situ perfused preparation'). The adrenocortical responses were measured directly in samples serially taken from the left adrenal vein. 3. Tested ACTH signals were either impulses (injections of 0-05--1-2 mu. ACTH) or step functions (constant infusions of 0-025--1-6 mu. ACTH/min). 4. All responses showed a 3-6 min delay, larger delays corresponding to smaller input signals. The step responses reached steady-state level without overshoot. 5. The impulse responses of the isolated perfused and of the intact infused glands, as well as their step responses, were similar as to dynamic form. 6. It is concluded that there is an inherent delay in the responses of both the isolated perfused and of the intact infused rat adrenal gland. Further, unlike what has been reported for the canine adrenal gland, the intact rat adrenal gland does not appear to be appreciably 'faster' in its response than the isolated gland. Finally, the

E Papaikonomou, J Physiology (1977)
adrenal gland: inherent delay in ACTH to CORT production

The PA subsystem:

Fix C (CRH) as input



$$\frac{dA}{dT} = p_A C f_A(OR) - d_A A$$

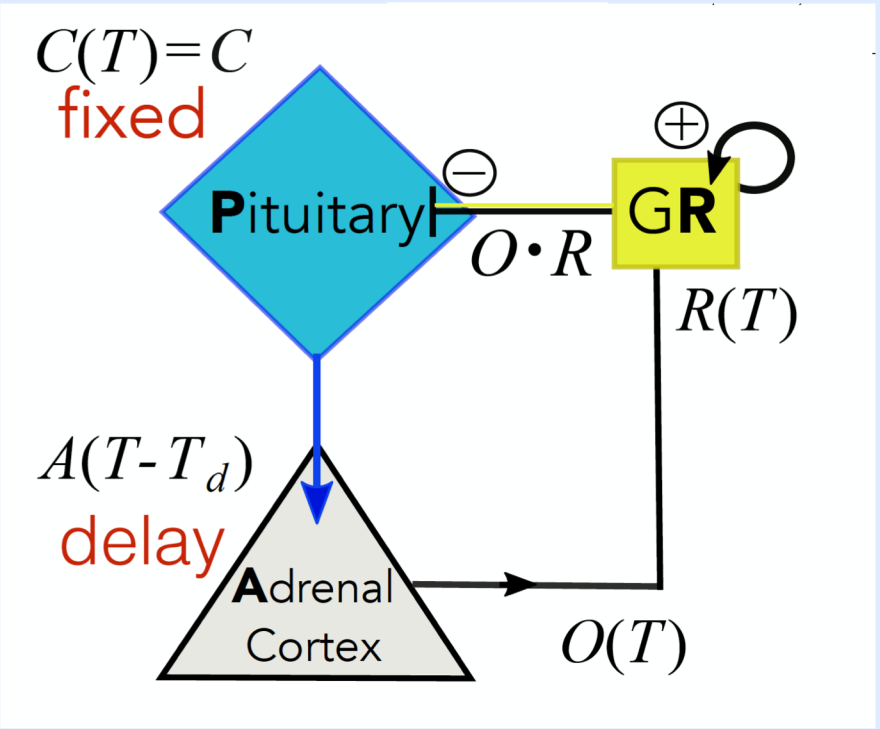
$$\frac{dO}{dT} = p_O A(T - T_d) - d_O O$$

$$\frac{dR}{dT} = p_R g_R(OR) - d_R R$$

C = CRH, A = ACTH, O = CORT, R= GR receptor

The PA subsystem:

Fix C (CRH) as input



$$\frac{dA}{dT} = p_A C f_A(OR) - d_A A$$

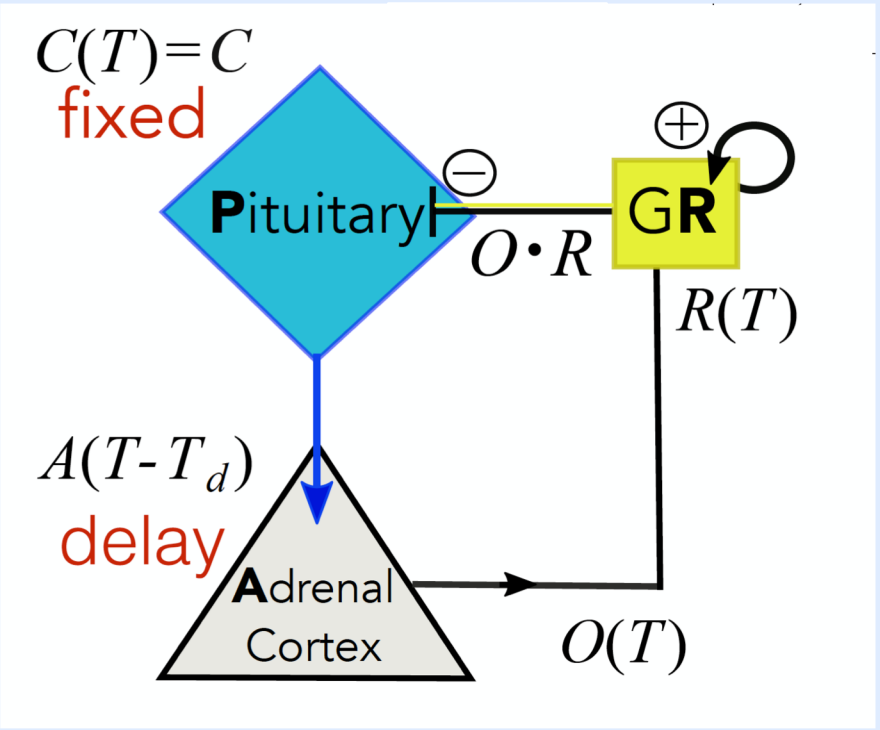
$$\frac{dO}{dT} = p_O A(T - T_d) - d_O O$$

$$\frac{dR}{dT} = p_R g_R(OR) - d_R R$$

f_A, g_R= functions of cortisol and GR receptor concentrations OR

The PA subsystem:

Fix C (CRH) as input



$$\frac{dA}{dT} = p_A C f_A(OR) - d_A A$$

$$\frac{dO}{dT} = p_O A(T - T_d) - d_O O$$

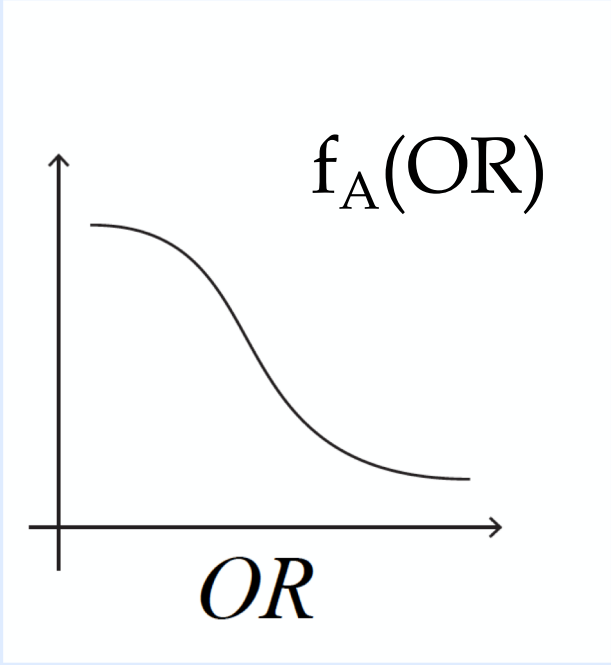
$$\frac{dR}{dT} = p_R g_R(OR) - d_R R$$

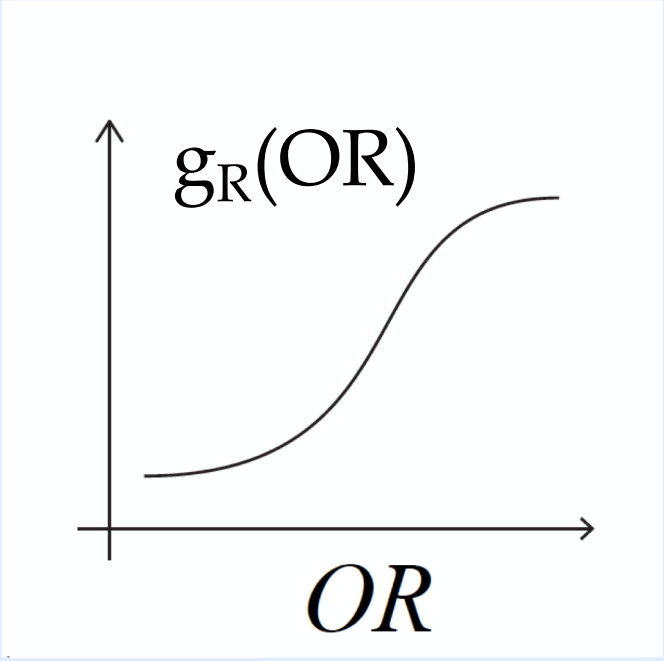
stimulate/decay/delay/feedback

Forms for g_A, f_A

f_A negative effect of cortisol-GR complex on ACTH production, positive and decreasing

g_R self-upregulation of cortisol-GR complex on GR production in pituitary, positive and increasing





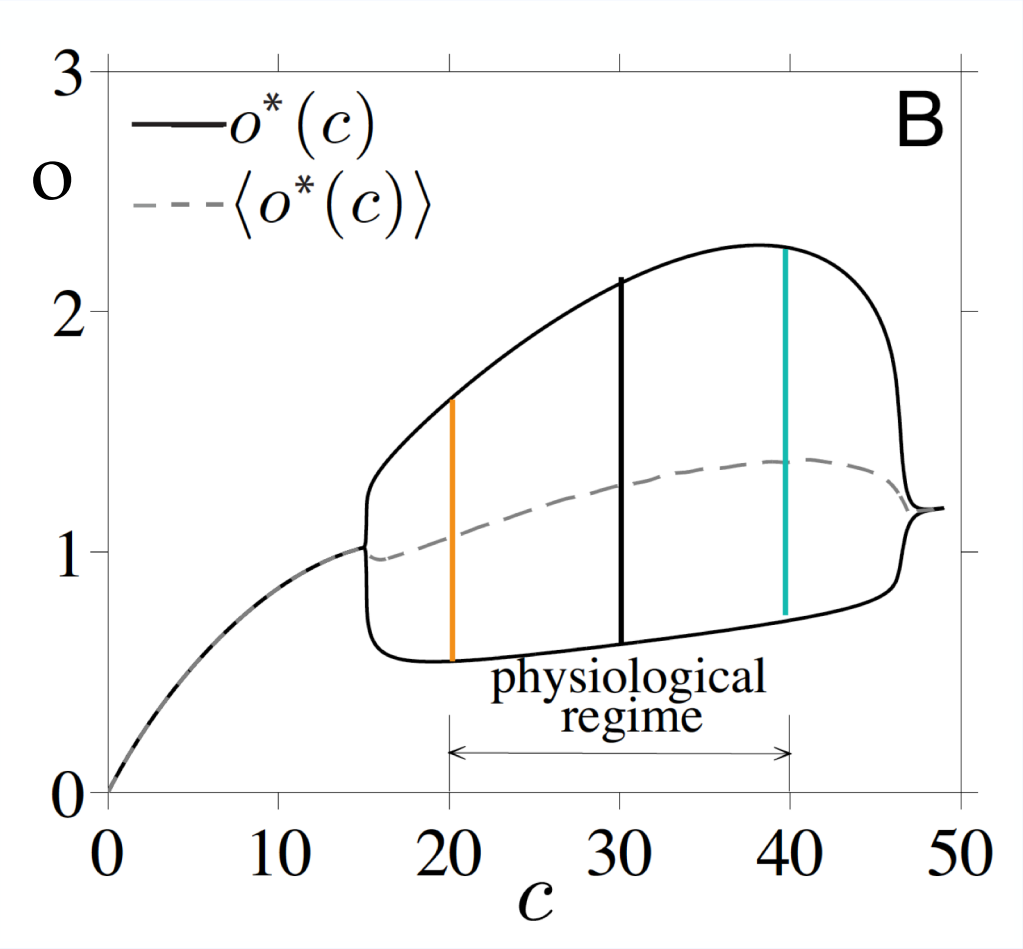
Parameters

Parameter	Value	Source and Ref.	Description
n	5	Assumed	Hill coefficient in upregulation function $g_c(c)$
$\bar{c}_\infty$	0.2	Estimated from [22]	Baseline stored CRH level
b	0.6	Estimated from [22]	Relates cortisol to stored CRH level
k	Undetermined	·	Relates stored CRH to CRH release rate
μ_c	Undetermined	·	Basal CRH release rate
q_0	Undetermined	·	Maximum CRH release rate
q_1^{-1}	Undetermined	·	Circulating CRH for half-maximum self-upregulation
q_2	1.8	Estimated from [21]	Ratio of CRH and cortisol decay rates
p_2^{-1}	0.067	p_2^{-1} [13]	(o r)-complex level for half-maximum feedback
p_3	7.2	p_3 [13]	Ratio of ACTH and cortisol decay rates
p_4	0.05	p_4 [13]	(o r)-complex level for half-maximum upregulation
p_5	0.11	p_5 [13]	Basal GR production rate by pituitary
p_6	2.9	p_6 [13]	Ratio of GR and cortisol decay rates
t_c	69.3	Assumed	CRH biosynthesis timescale
t_d	1.44	"τ" [13]	Delay in ACTH-activated cortisol release

"Free parameters" – variability in individual patients
HPA - highly conserved

Simulate – c constant

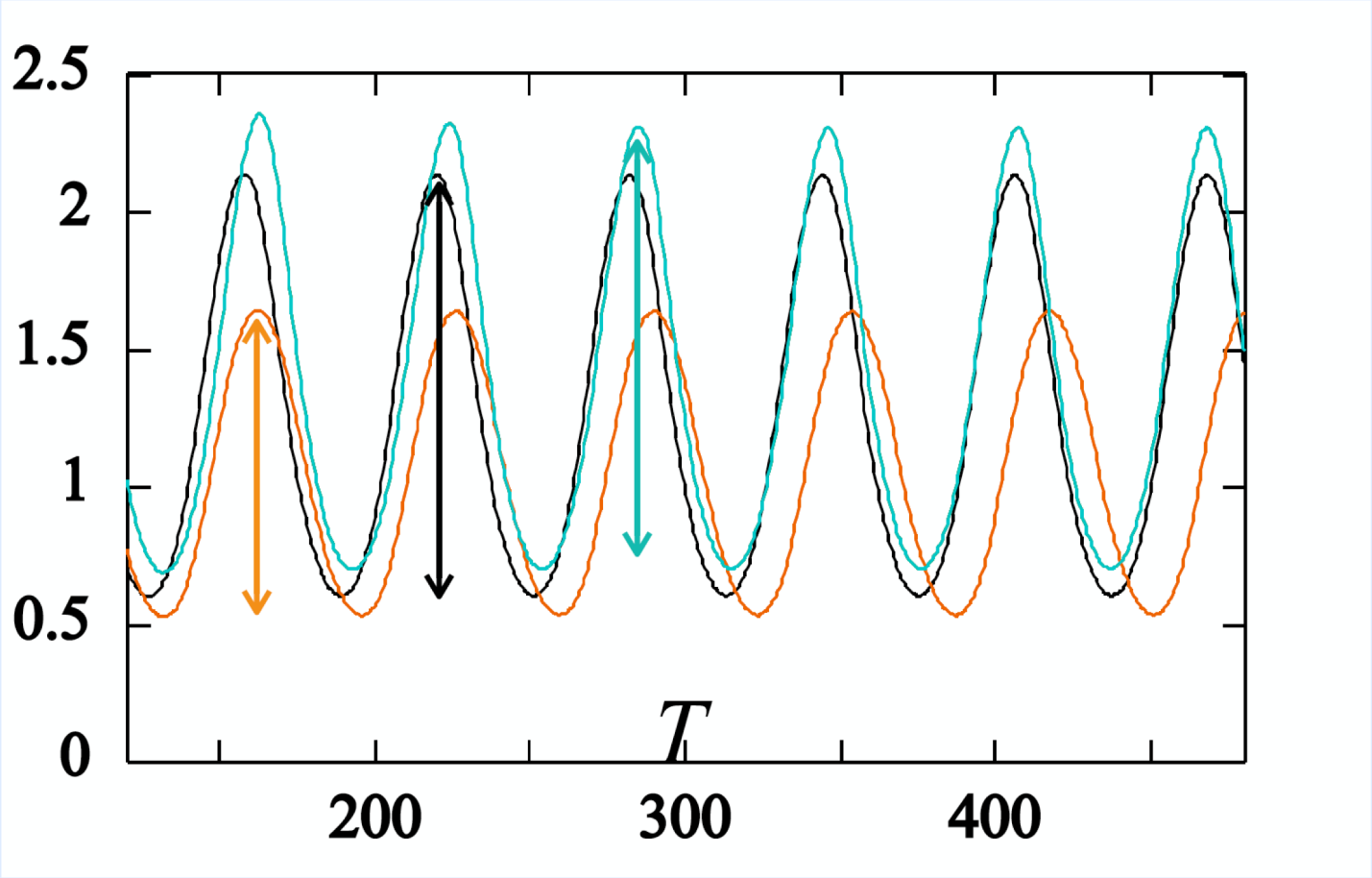
Use relevant parameters, fix undetermined ones, non-dimensionalize and change c



Mean and amplitude of cortisol o change with c

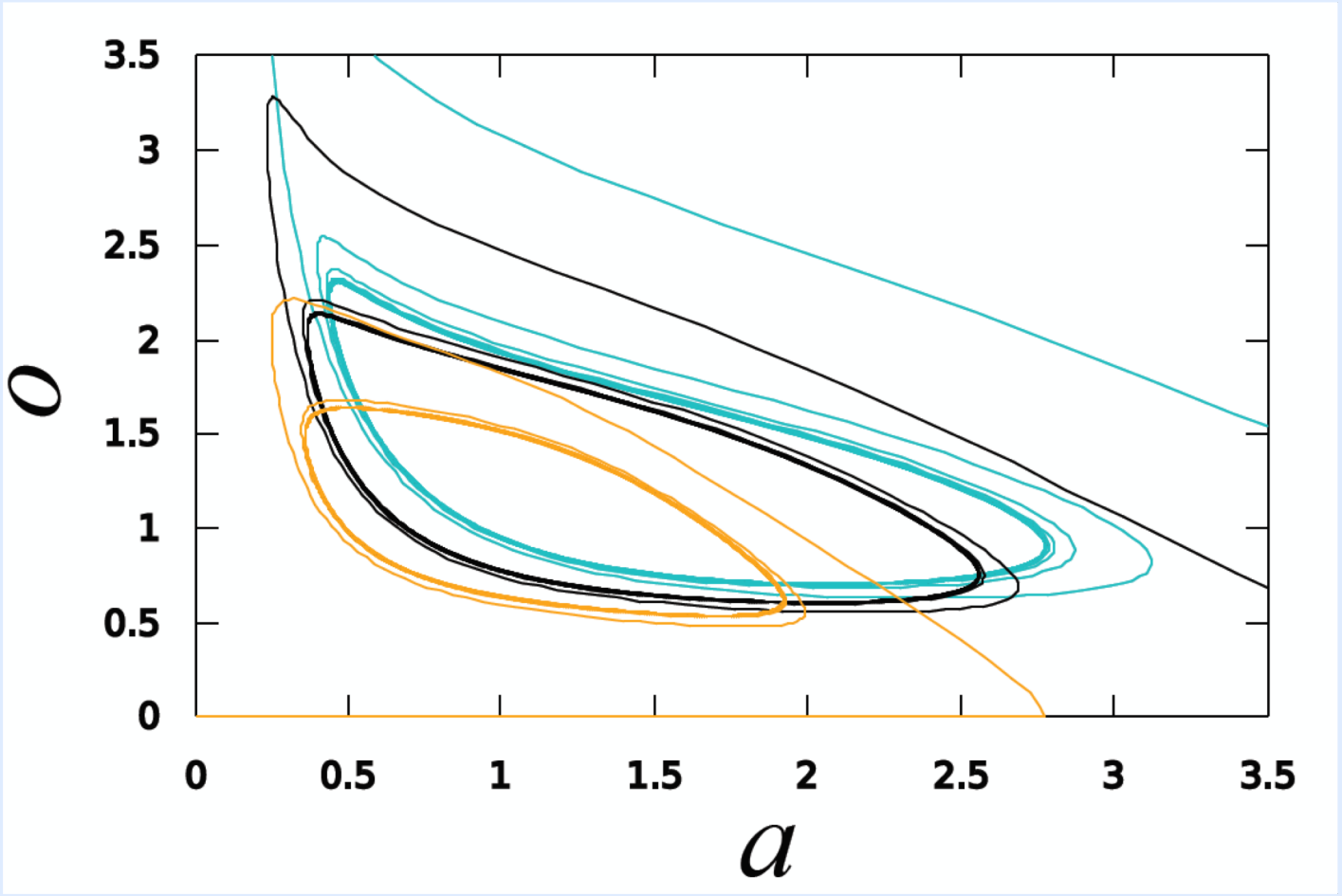
Simulate

$o(T)$



c=20, c=30, *c=40*

Simulate



c=20, c=30, c=40

What do we want from this model?

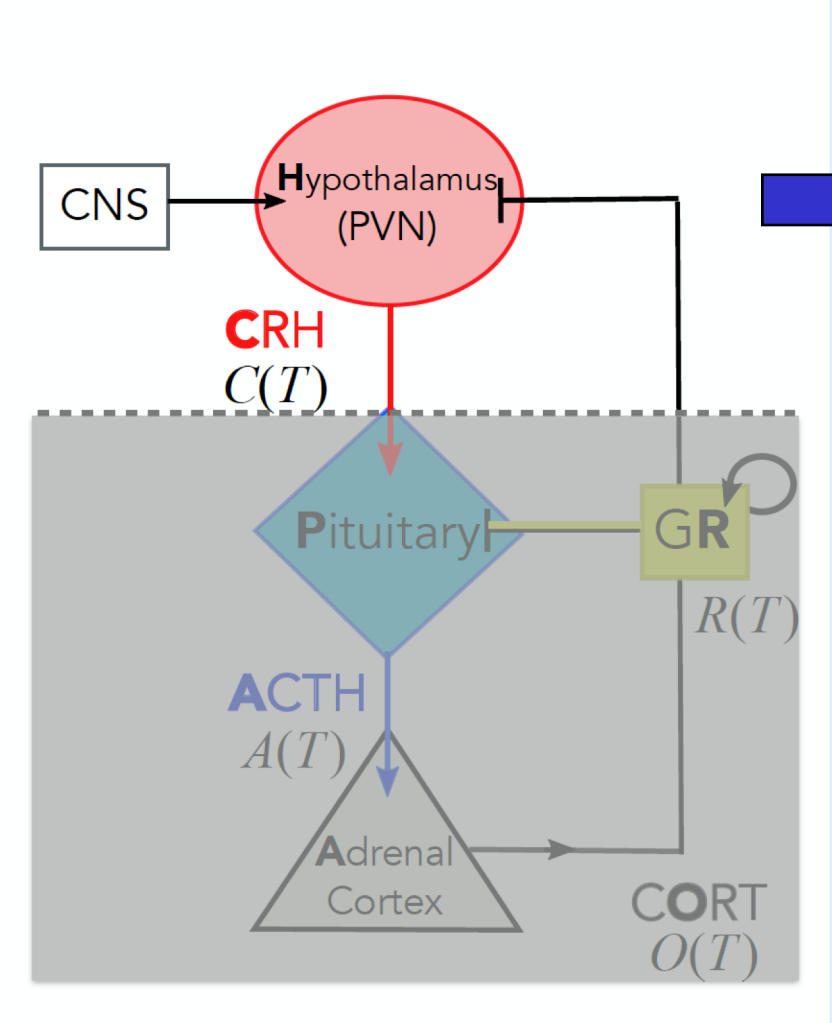
1. Steady states with “low” cortisol (diseased state) and “high” cortisol (normal state)

“hypocortisolism”

Reproduce realistic features such as oscillations in cortisol (and ACTH – no oscillations in CRH)

Let’s add CRH dynamics

Stored and released CRH



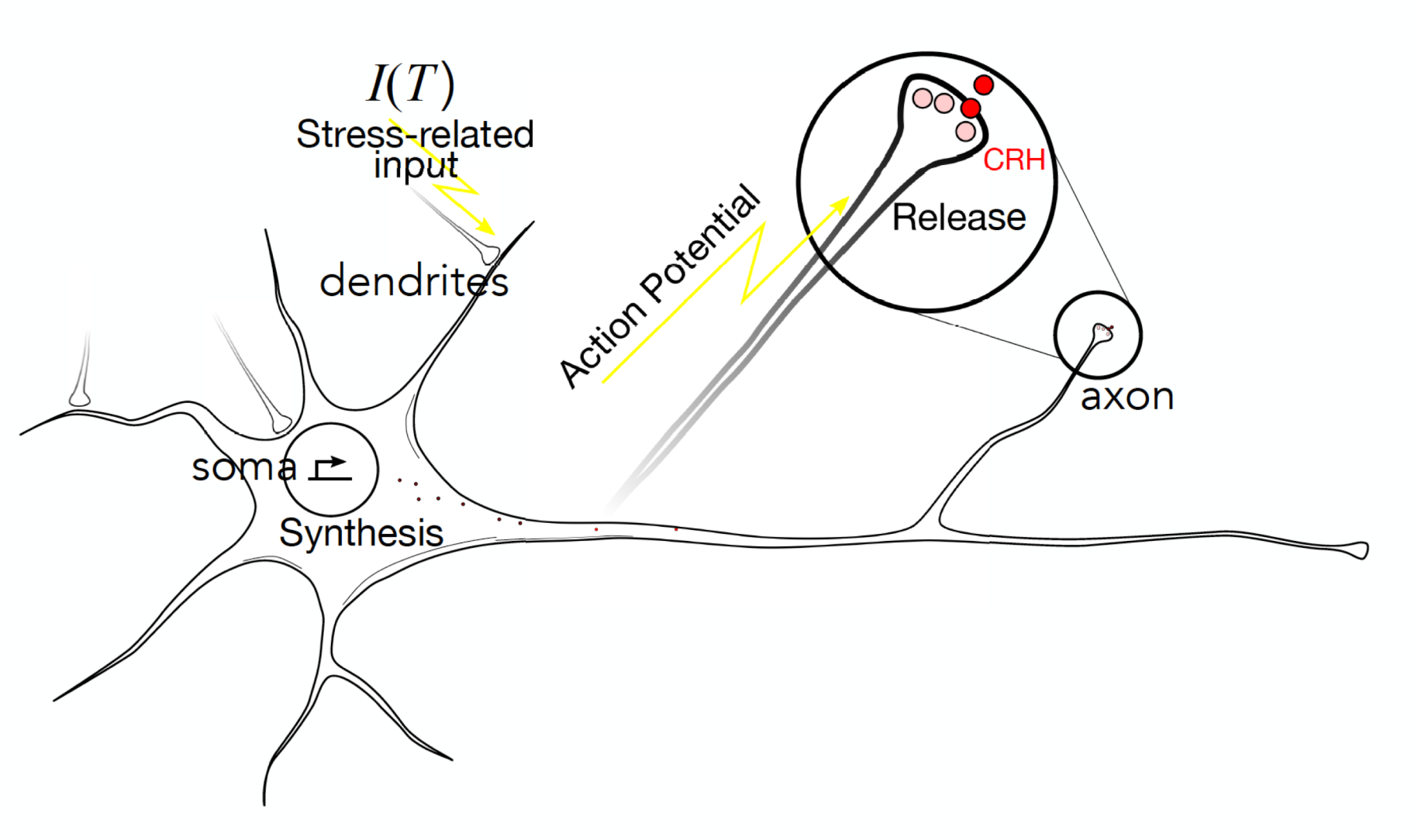
CRH is stored within neurons in the PVN

$C_s(T)$

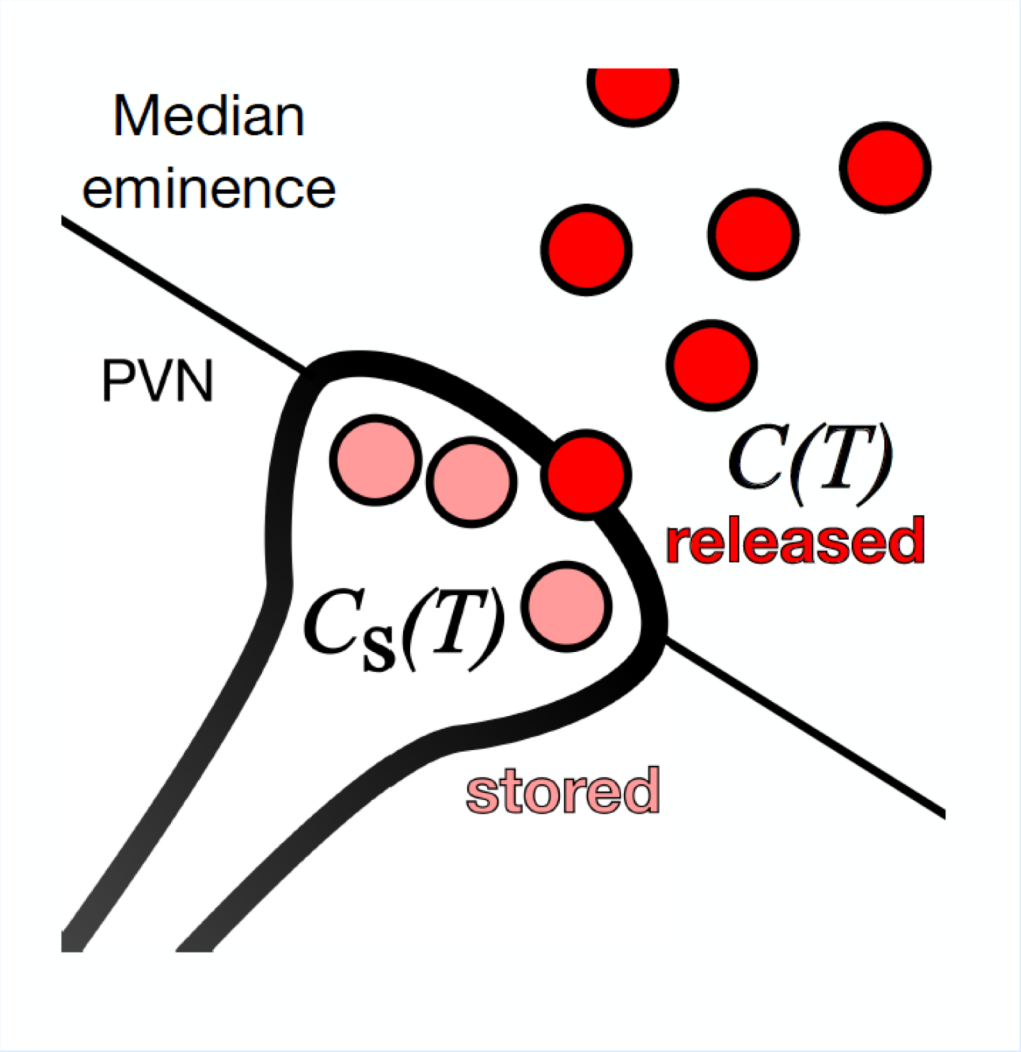
CRH is released upon stimulation

$C(T)$

Neuronal activity



Stored CRH C_s



CRH is stored within neurons in the PVN $C_s(T)$

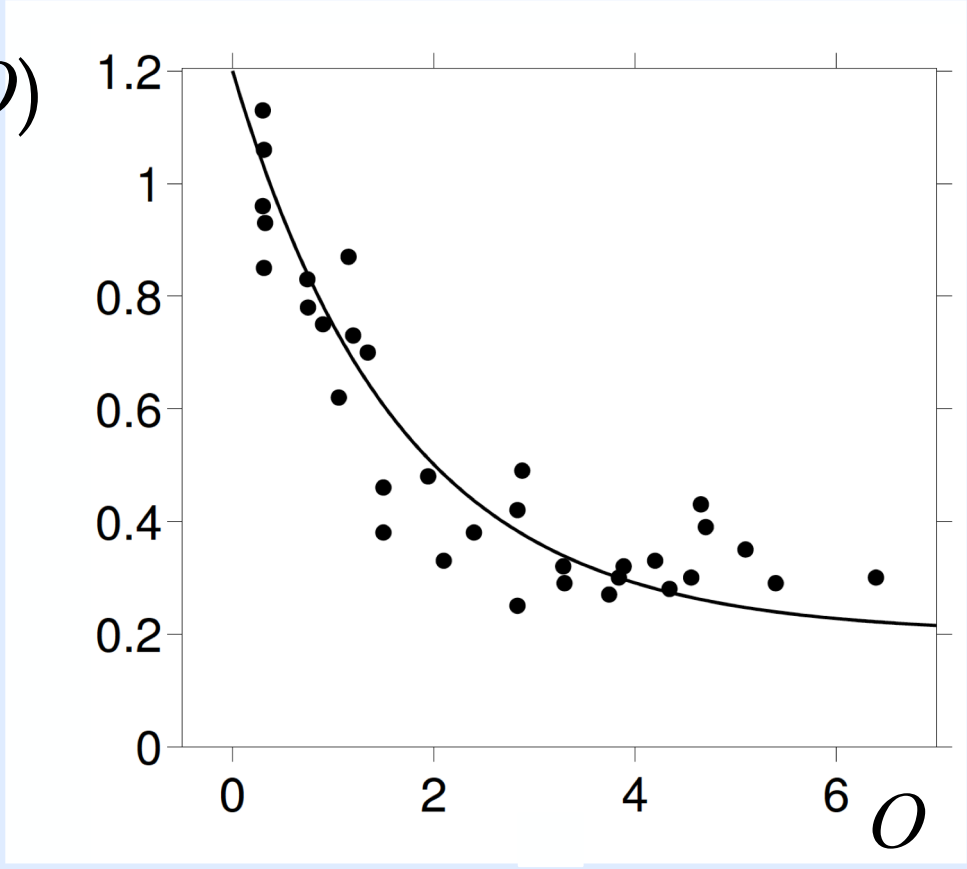
CRH is released upon stimulation

The amount of stored CRH depends on cortisol

Cortisol: negative feedback on CRH synthesis

Cortisol injected into adrenalectomized rats for 5-7 days

$C_\infty(O)$

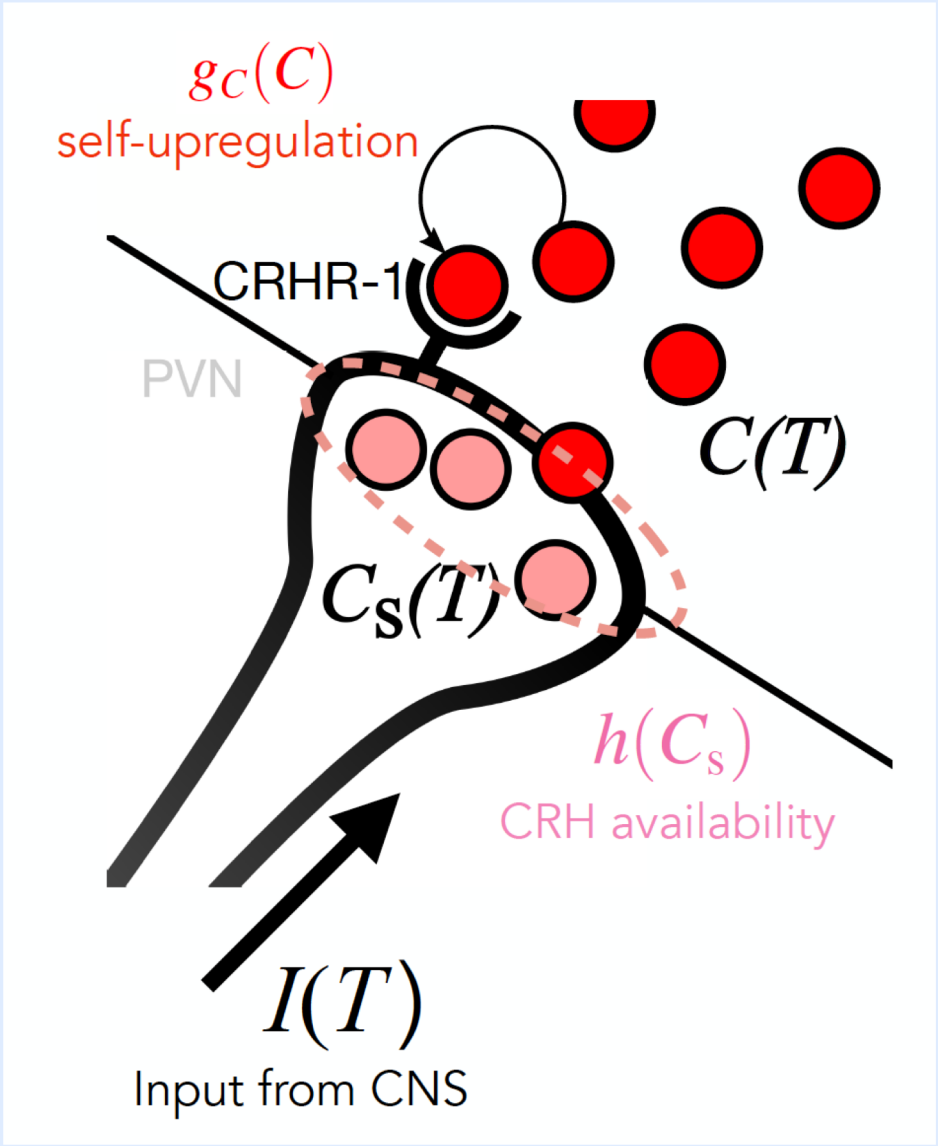


$$C_\infty(O) = \bar{C}_\infty + e^{-bO}$$

$$\frac{dC_s}{dT} = \frac{C_\infty(O) - C_s}{T_C}$$

T_c = 12 hours time for stored CRH to relax to $C_s = C_\infty$

Released CRH C



Released CRH depends on

1. Input from CNS $I(T)$

2. Available stored CRH $h(C_s)$

3. Already present CRH $g_c(C)$

self - upregulation

Self upregulation of CRH

Proc Natl Acad Sci U S A. 1985 Nov;82(22):7787-90.

Effects of intravenous and intraventricular injection of antisera directed against corticotropin-releasing factor on the secretion of anterior pituitary hormones.

Ono N, Samson WK, McDonald JK, Lumpkin MD, Bedran de Castro JC, McCann SM.

Abstract

To determine the physiological significance of corticotropin-releasing factor (CRF) in the control of pituitary hormone secretion, highly specific antibodies directed against the peptide were injected either intravenously or intraventricularly (third ventricle) and the effect on plasma levels of pituitary hormones was determined before and after application of ether stress for 1 min. The intravenous injection of CRF antiserum (0.5 ml) did not significantly alter basal corticotropin (ACTH) levels in freely moving ovariectomized rats but largely blocked the increase in plasma ACTH resulting from ether stress. These antibodies had no effect on the ether-induced decline in plasma growth hormone (GH), and they failed to modify plasma luteinizing hormone levels. In a second experiment, CRF antiserum (3 microliter) or normal rabbit serum was injected into the third ventricle. A blood sample was drawn 24 hr later and immediately thereafter another injection of CRF antiserum or normal rabbit serum was made. There was no modification in the level of any of the hormones 24 hr after the first injections, and they were similar in CRF antiserum and normal rabbit serum-injected animals. After imposition of ether stress, the response of plasma ACTH was nearly completely blocked by the intraventricular CRF antiserum, but the degree of blockade was slightly less than that obtained by intravenous injection. The decline in plasma GH after ether stress was blocked by the intraventricular CRF antiserum. There was no effect of the intraventricular injection of the antiserum on the levels of the other pituitary hormones. The results with intravenous injection of the antisera indicate that CRF plays an extremely important but probably not completely indispensable role in the release of ACTH after ether stress. The results of the intraventricular injection of the antiserum suggest strongly that endogenous CRF may also modify its own release in response to stress, augmenting it by a positive ultrashort loop feedback, and that the antisera against the peptide blocked this action; however, an action at the pituitary of these intraventricularly injected antibodies cannot be completely ruled out. The blockade of the stress-induced suppression of GH release by the CRF antibodies suggests that CRF released intrahypothalamically during ether stress brings about an alteration in the hypothalamic control of GH secretion such that the stress-induced inhibition of GH release is blocked.

Positive feedback

Released CRH *C*

$$\frac{dC}{dT} = p_C I(T) h(C_s) g_c(C) - d_c C$$

$$h(C_s) = 1 - e^{-kC_s}$$

$$g_c(C) = 1 - \frac{\mu_c K_c^n}{K_c^n + C^n}$$

low C_s → $h(C_s) = 0$ high C_s → $h(C_s) = 1$

low C → $g_c(C) = 1\text{-}\mu_c$ high C → $g_c(C) = 1$

Full problem – non dimensional

SLOW

FAST

$$
\begin{cases}
\dfrac{\mathrm{d}c_\mathrm{s}}{\mathrm{d}t} = \dfrac{c_\infty(o) - c_\mathrm{s}}{t_c}, \\
\dfrac{\mathrm{d}c}{\mathrm{d}t} = q_0 I(t) h(c_\mathrm{s}) g_c(c) - q_2 c, \\
\dfrac{\mathrm{d}a}{\mathrm{d}t} = \dfrac{c}{1 + p_2(or)} - p_3 a, \\
\dfrac{\mathrm{d}o}{\mathrm{d}t} = a(t - t_\mathrm{d}) - o, \\
\dfrac{\mathrm{d}r}{\mathrm{d}t} = \dfrac{(or)^2}{p_4 + (or)^2} + p_5 - p_6 a.
\end{cases}
$$

Determine behavior (c, c_s, a, o, r) at
"steady state"
given a fixed input $I = I_0$

Once c is known,
a,o,r are also known

Determine behavior (c, c_s, a, o, r) at "steady state" given a fixed input $I = I_0$

Once c is known, a, o, r are also known

Bistability in CRH release

$$\frac{dc}{dt} = p_C I(t) h(c_s) g_c(c) - q_2 c$$

"q"

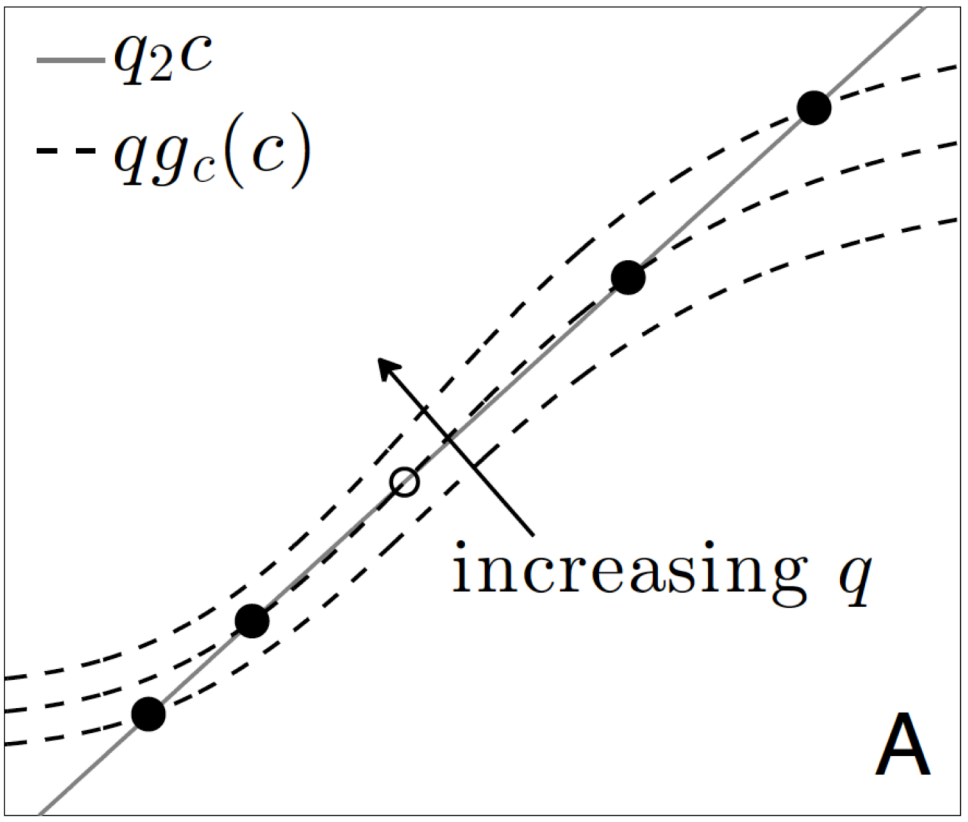
fixed input $I(t) = I_0$

Since c_s is slow, if we look at the "fast dynamics" with c_s fixed – q can be seen as a bifurcation parameter

For fixed q we can find the nullclines of c

$$0 = q g_c(c) - q_2 c$$

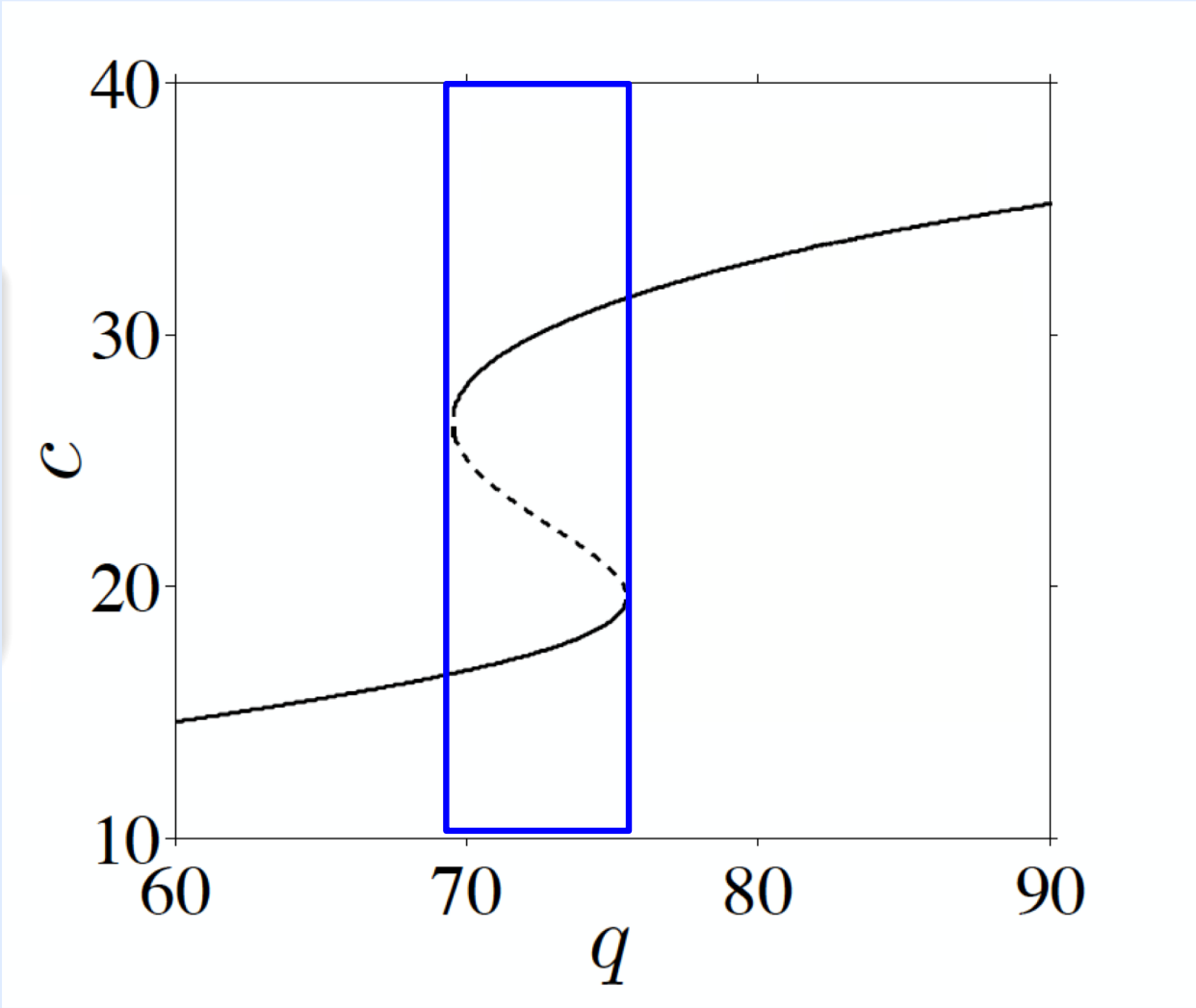
Bistability in CRH release



$$0 = q g_c(c) - q_2 c$$

One (stable) or three (two stable, one unstable) intersections depending on q

Bistability in CRH release

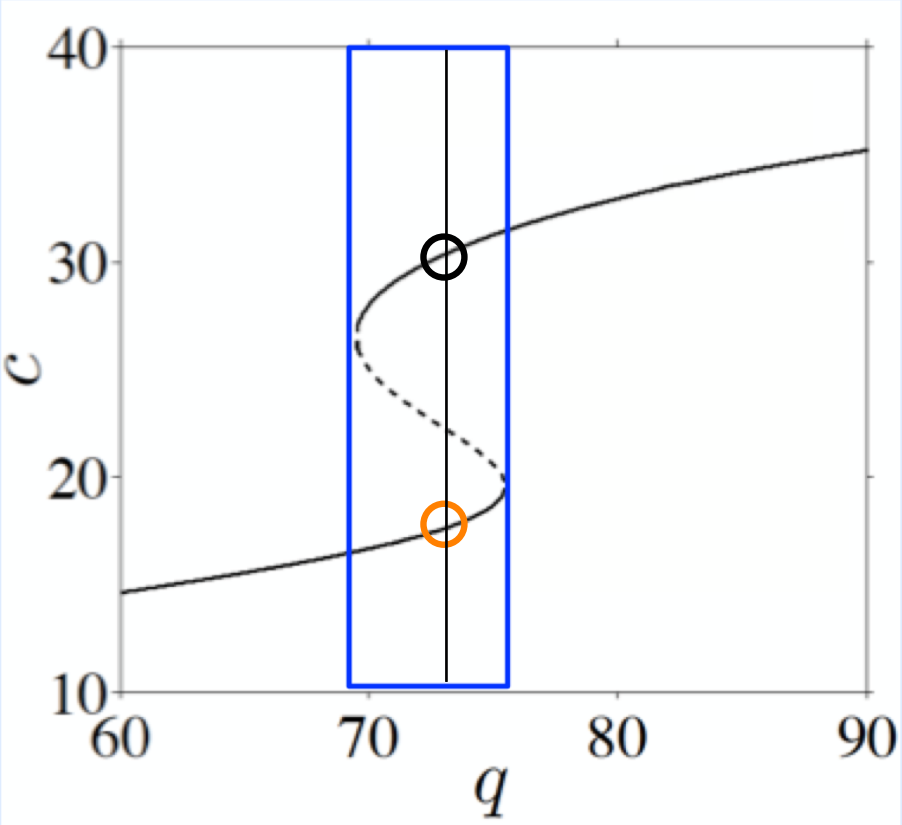


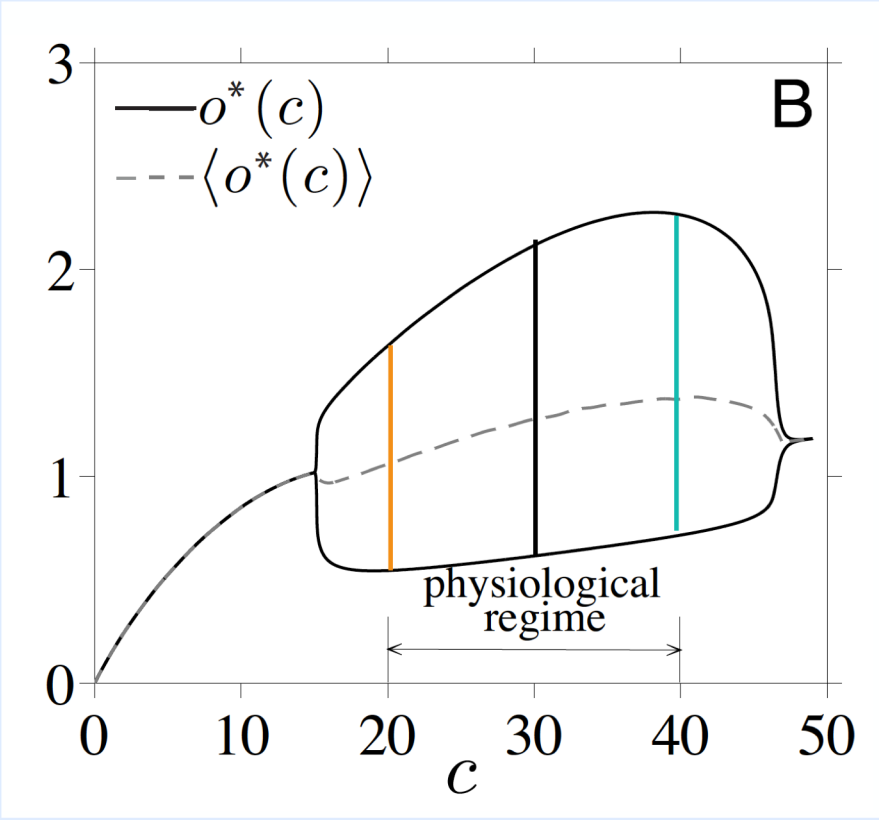
$$0 = qg_c(c) - q_2c$$

q bifurcation parameter controlling fast flow at short time

Bistability in CRH release

Once c is determined we can use the PA subsystem to determine the rest of the a-gr-o variables as shown above





What do we want from this model?

Reproduce realistic features such as oscillations in cortisol and ACTH

Steady states with “low” cortisol (diseased state) and “high” cortisol (normal state)

Mission accomplished!

What about $c_{\bar{s}}$?

Include slow dynamics

$$\frac{dc_s}{dt} = \frac{c_\infty(o) - c_s}{t_c} = 0$$

$$c_s \approx c_\infty(o(c)) \approx \langle c_\infty(c) \rangle \approx \int_0^{2\pi} c_\infty(o(\theta, c)) \frac{d\theta}{2\pi}$$

$c_s \rightarrow c_\infty(o)$ becomes $c_s(c)$

$I(t) = I_0$

$q(c_s) = p_c\, I(t)\, h(c_s) \rightarrow q(c) = p_c\, I_0\, h(c)$

Nullclines in (q,c)

FAST: $qg_c(c) - q_2 c = 0$

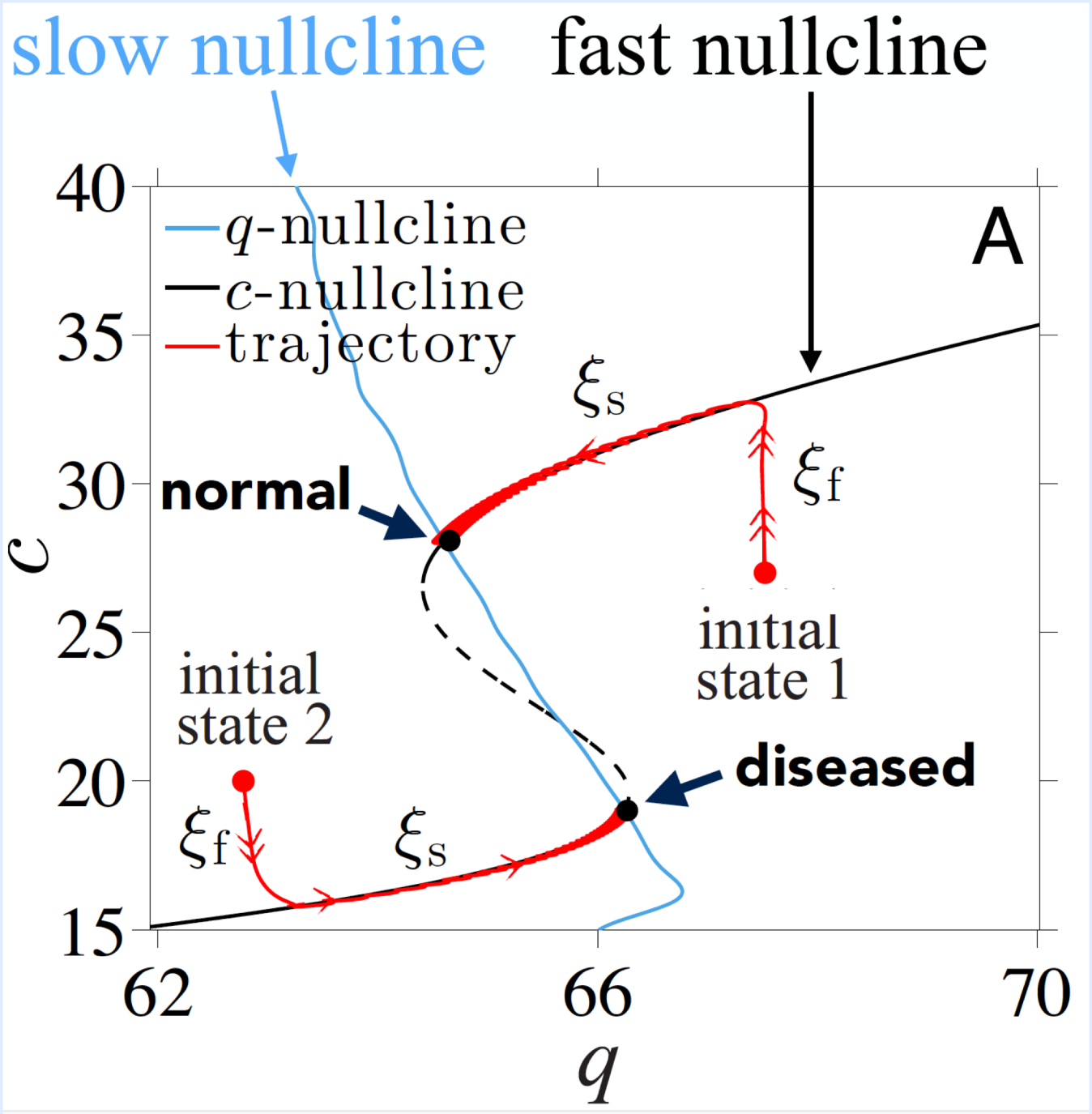
SLOW: $q = p_c I_0 h(c)$

Intersections yield (q,c)

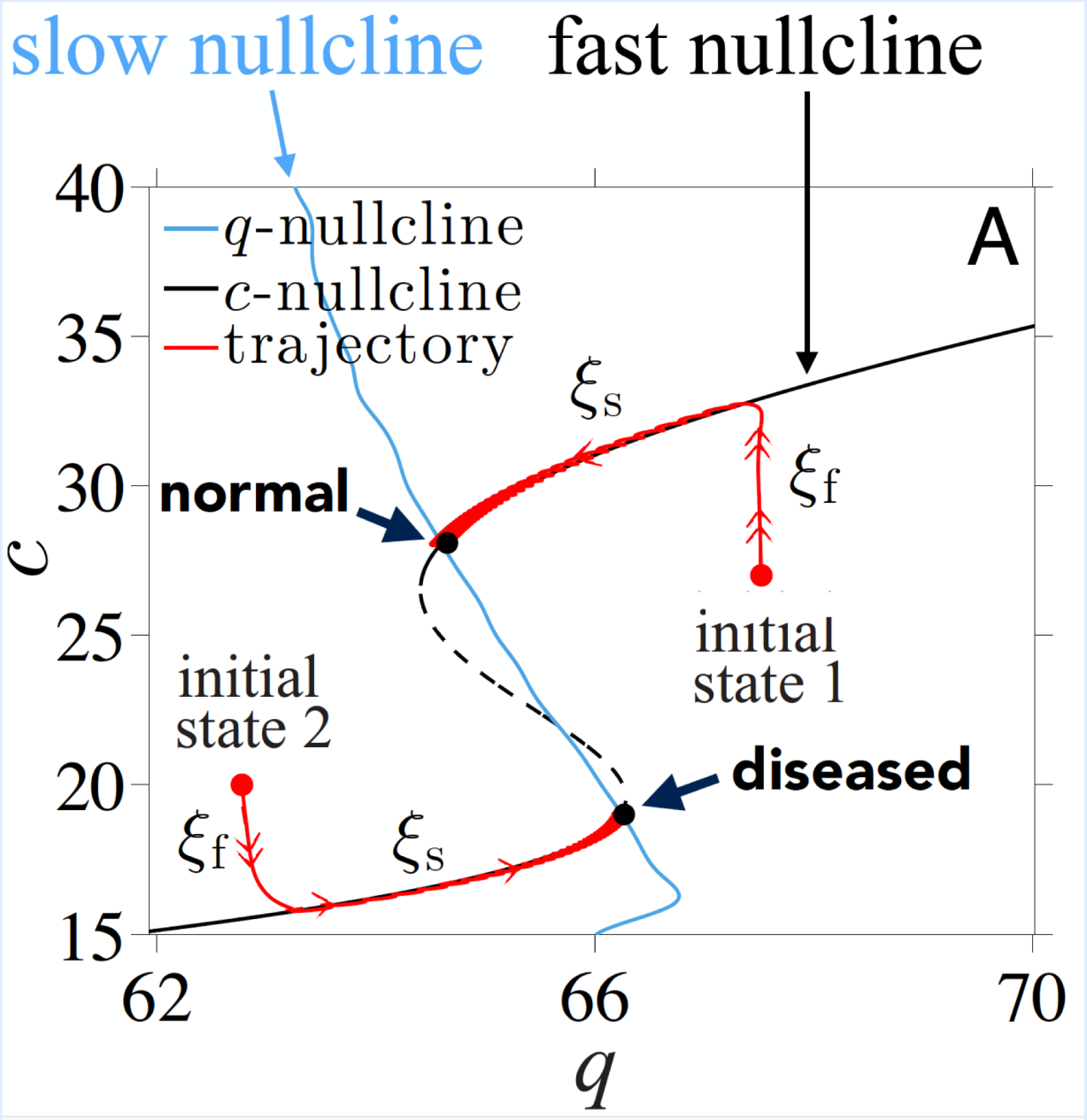
From c find (a,o,r)
From q find $h(c_s)$ and c_s

Full Dynamics?

q changes slowly
c changes fast


slow nullcline
fast nullcline
A
q-nullcline
c-nullcline
trajectory
normal
diseased
initial state 1
initial state 2
ξs
ξf
ξf
ξs
40
35
30
25
20
15
c
62
66
70
q

Full Dynamics

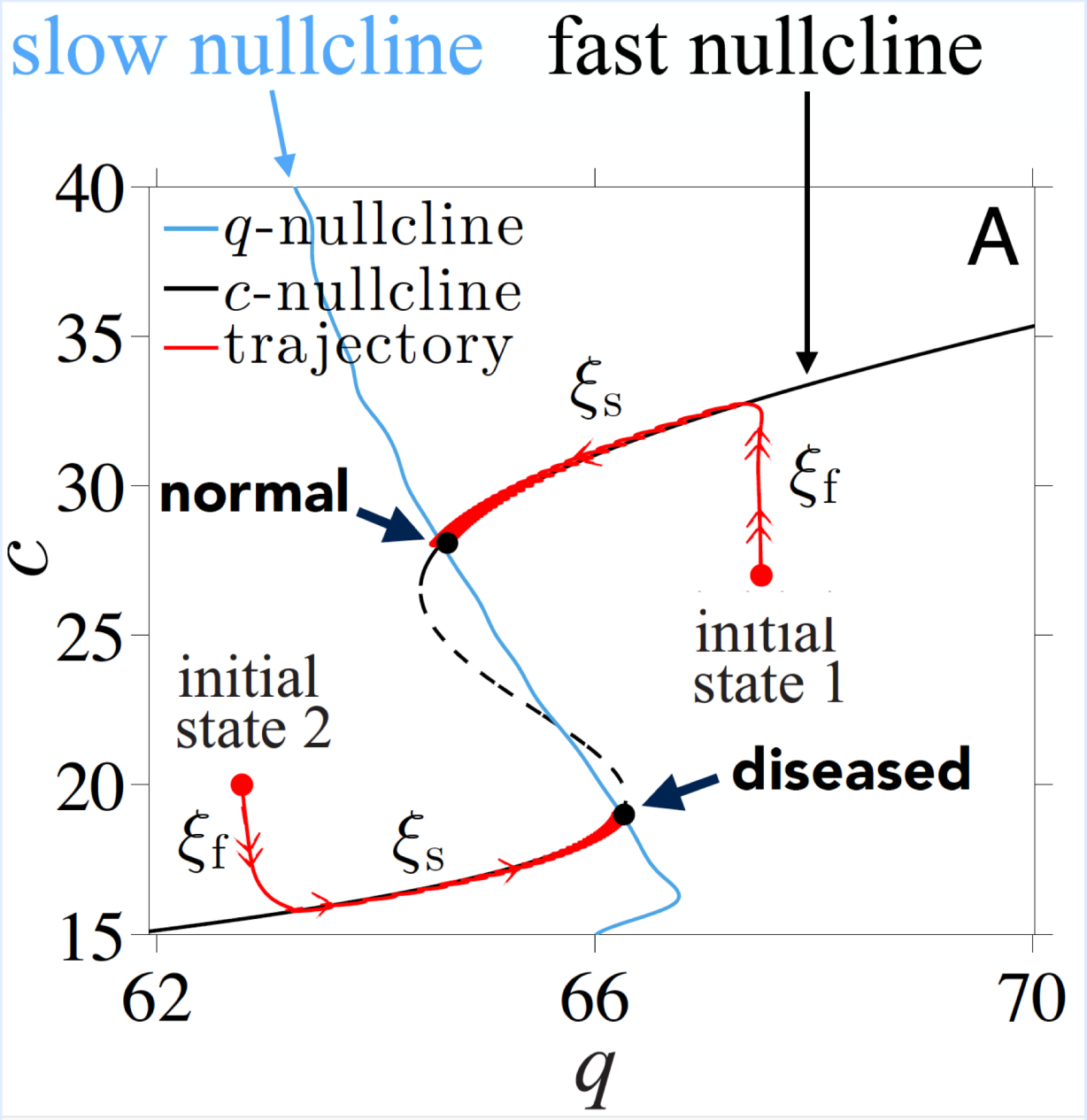


Two equilibrium states

Normal with higher c,o

Diseased with lower c,o

Initial State 1

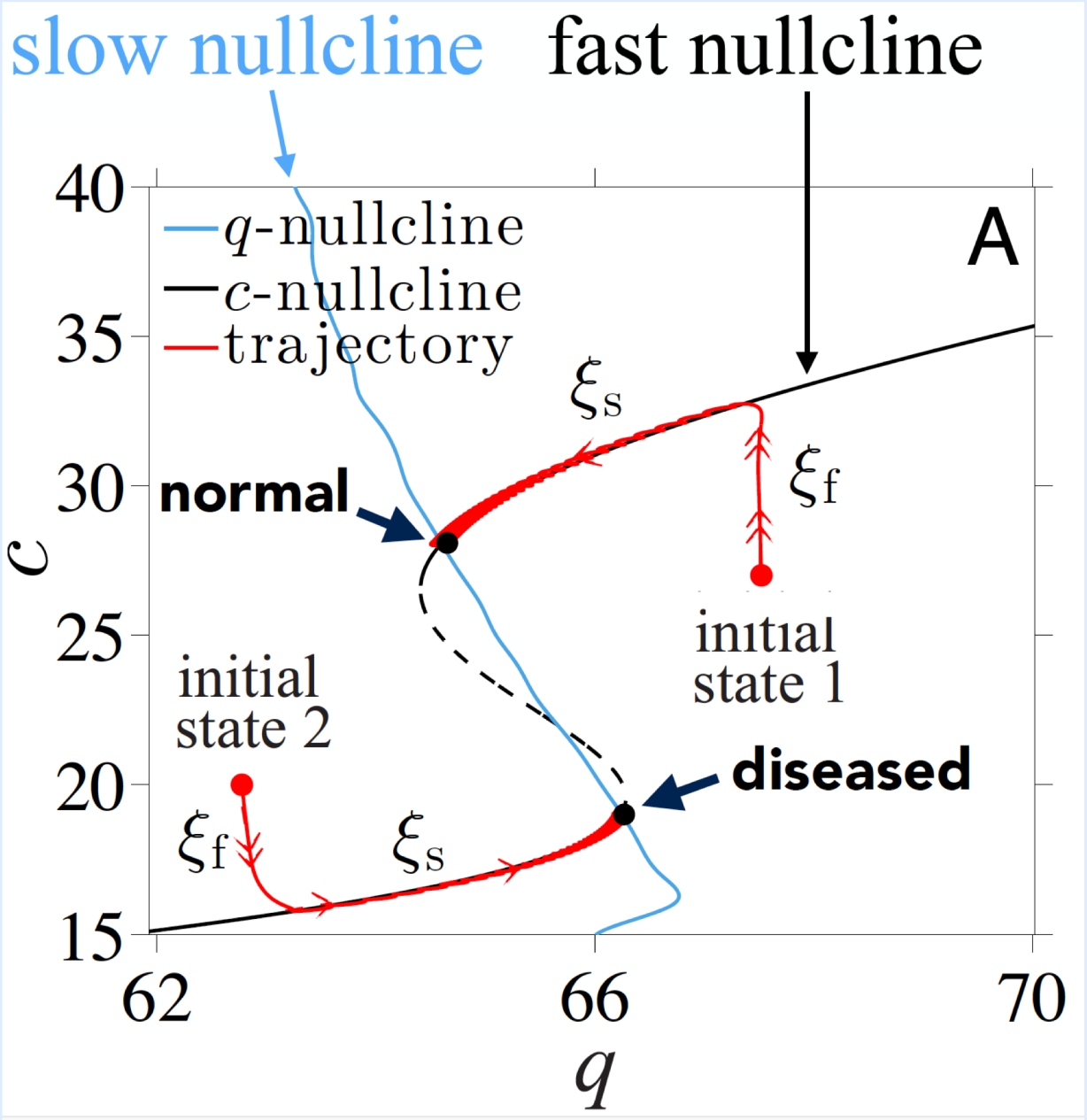


Quickly find the nearest "fast nullcline" with flow ξ_f

Slowly move along the "fast nullcline" with flow ξ_s

Reach **normal** state

Initial State 2



Quickly find the nearest "fast nullcline" with flow ξ_f

Slowly move along the "fast nullcline" with flow ξ_s

Reach **diseased** state

Normal to Diseased?

So far

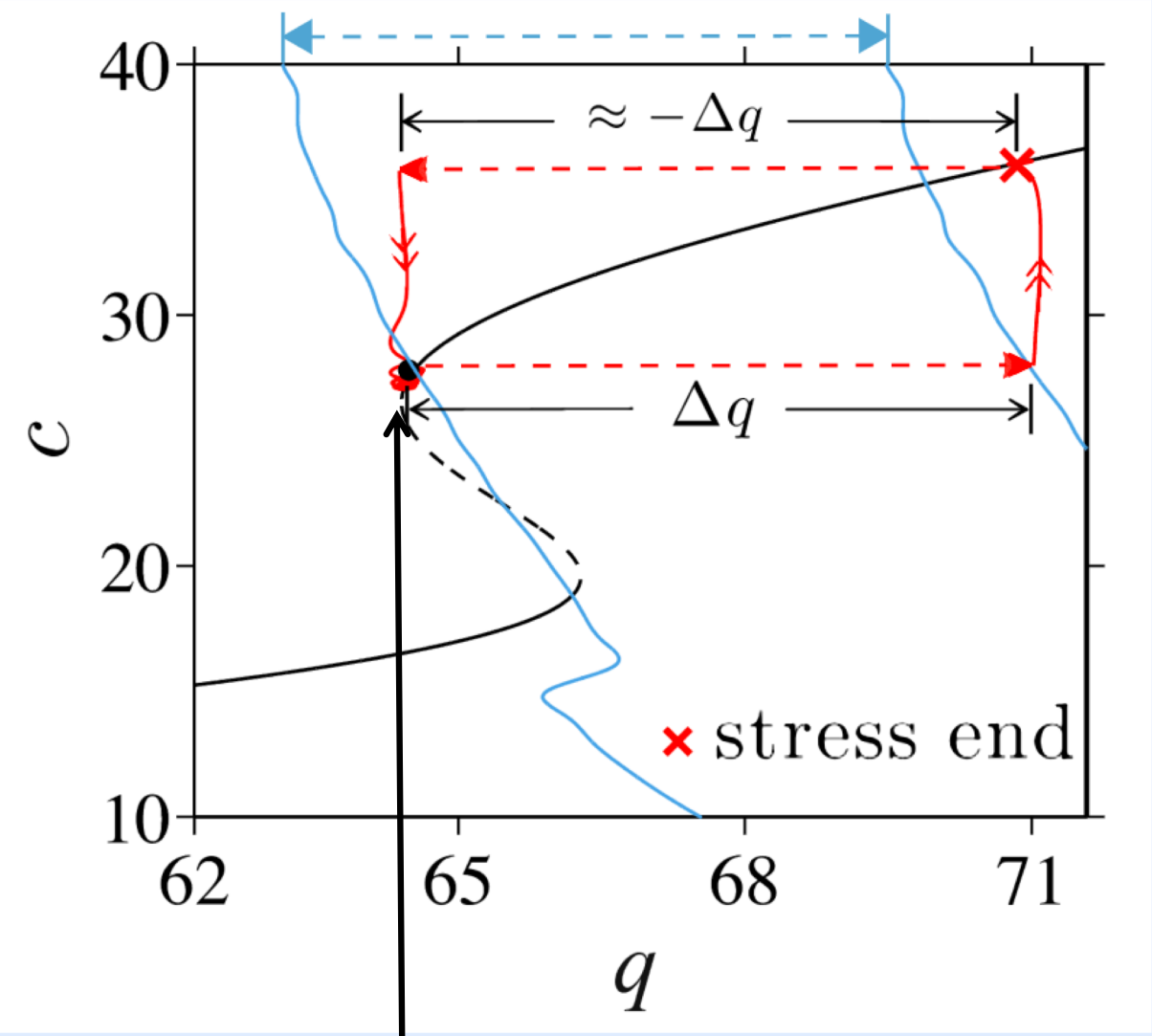
$$I(t) = I_0 = 1$$

What if we now change the stress level?

$$I(t) = I_0 + I_{ext}(t)$$

I_{ext} turned on for a finite amount of time

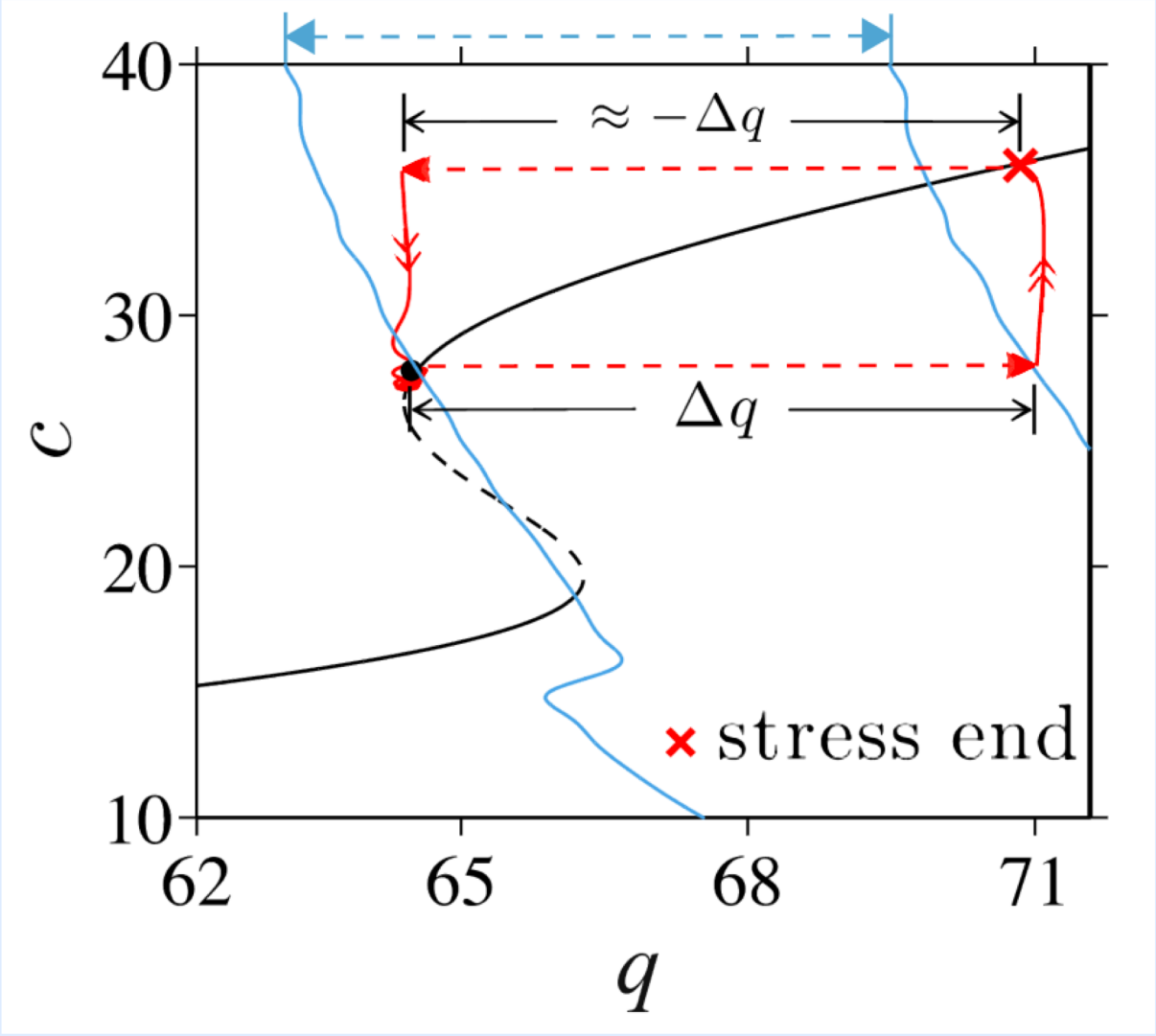
Normal response



Normal state, START turn on $I_{ext} = 0.1$

$$q = p_c\,(I+I_{ext})\,h(c_s(c))$$

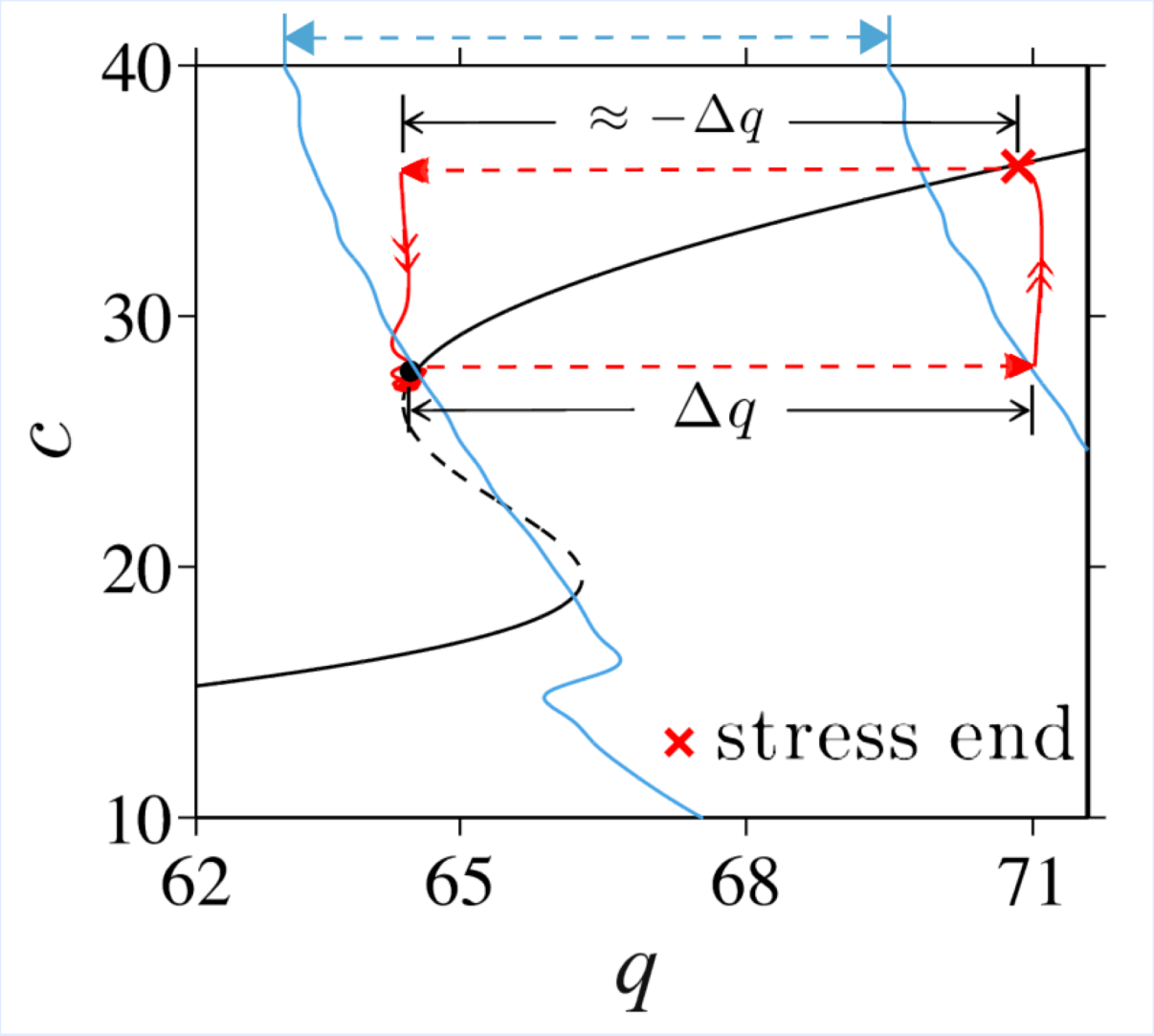
Turn off $I_0 + I_{ext} \rightarrow I_0$



The q nullcline will shift back towards its original location

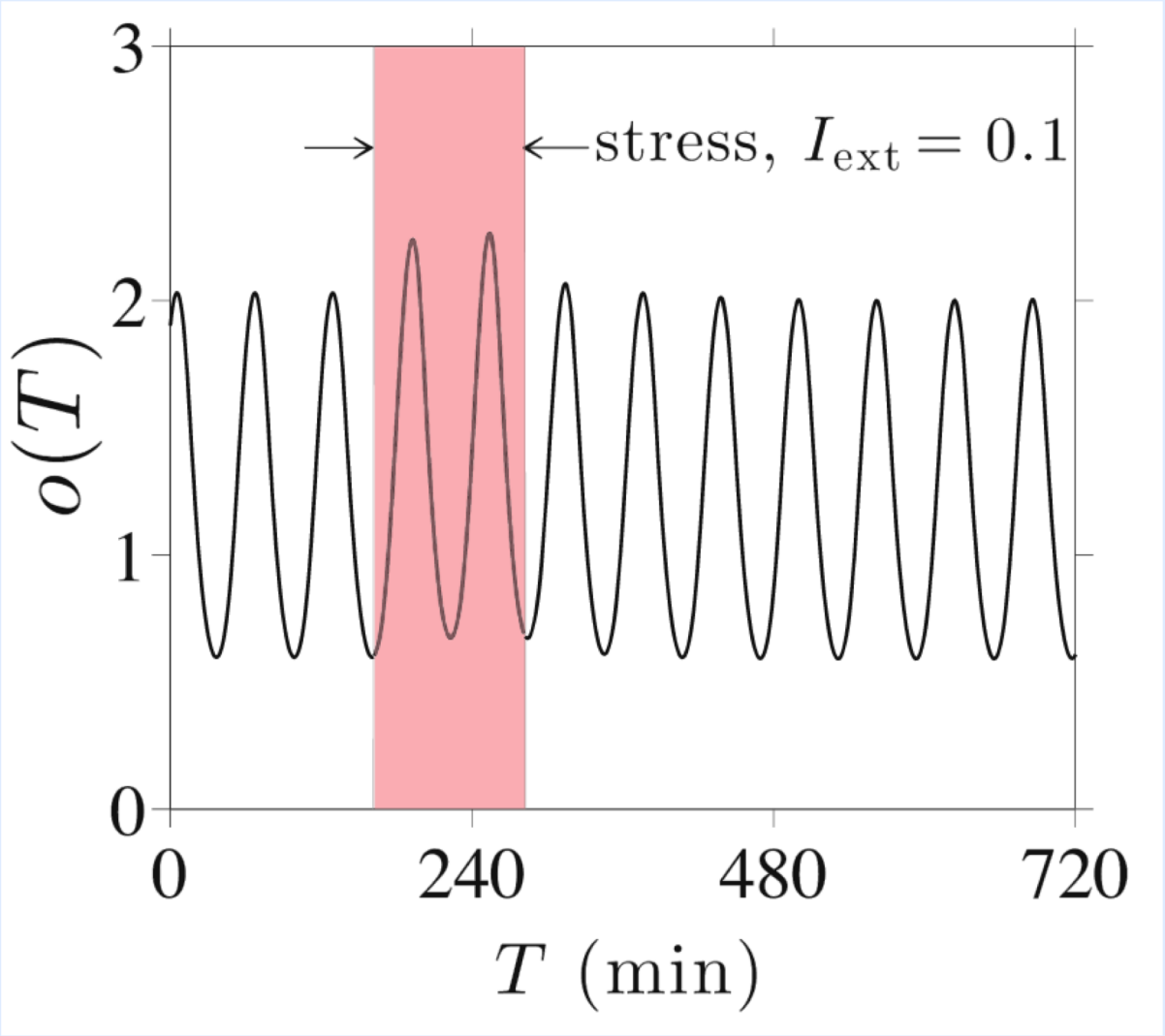
The system will move vertically towards the original, normal state

A temporary I_{ext} …



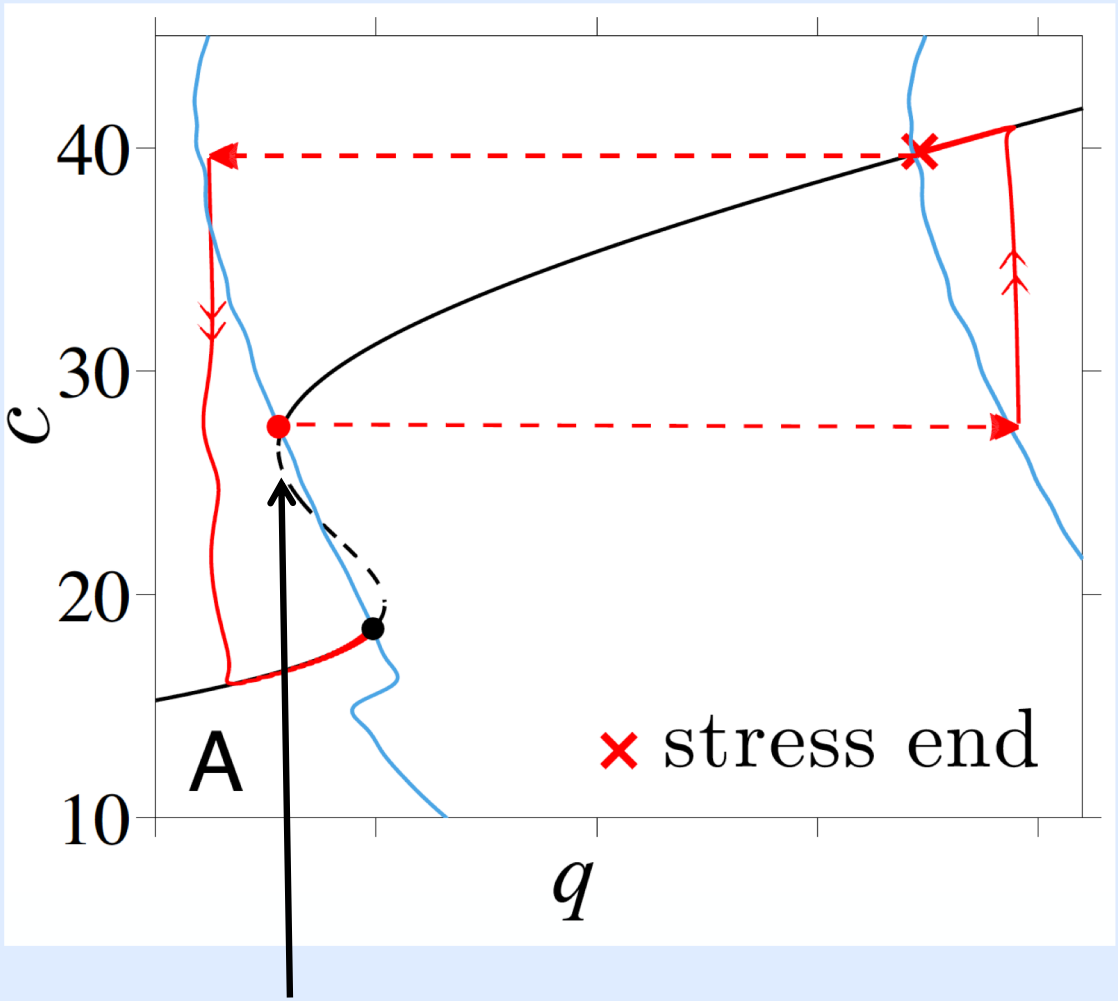
… returned the system back to its original state
normal response – two hours of external stress

Cortisol for I_{ext} =0.1; stress for 2 hs



The system returns back to its original state

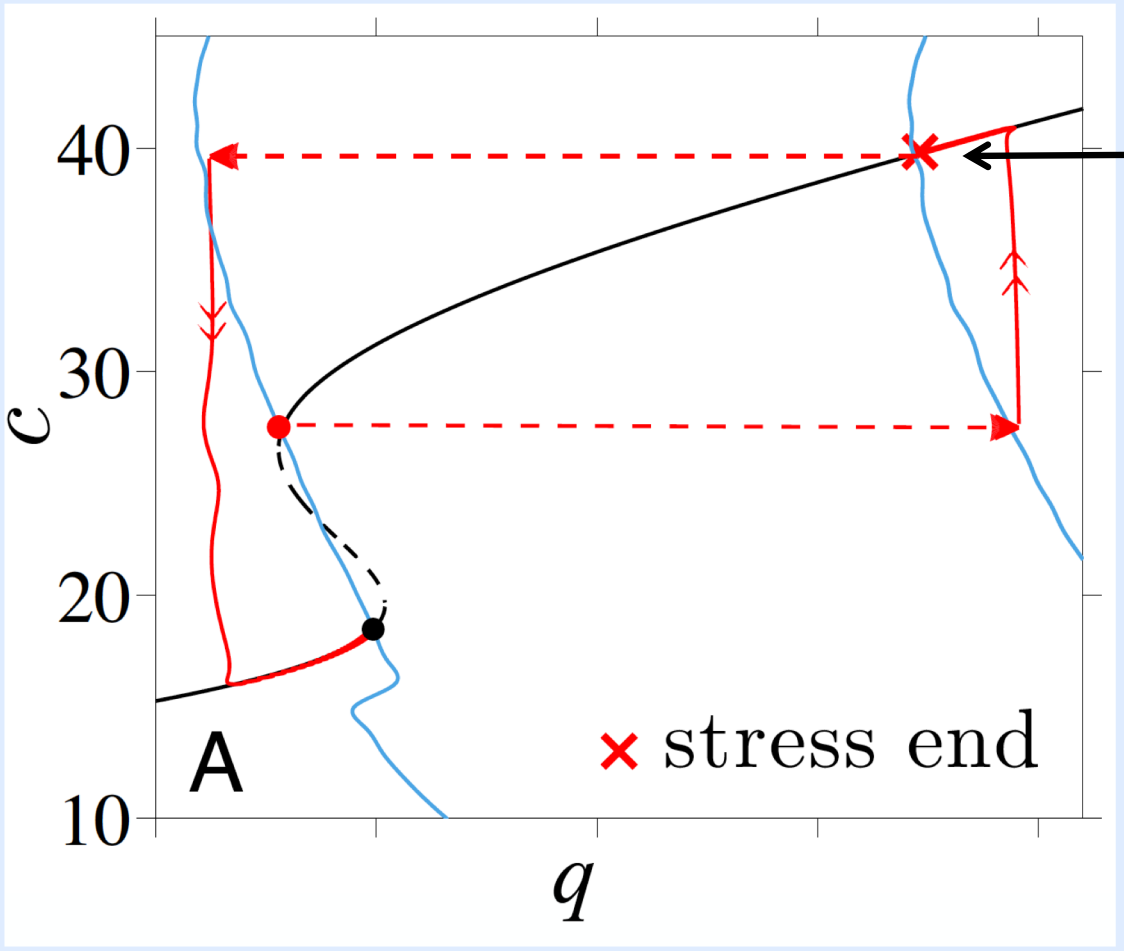
Normal to Diseased?



Normal state, START turn on I_{ext}

$$q = p_c\,(I+I_{ext})\,h(c_s(c))$$

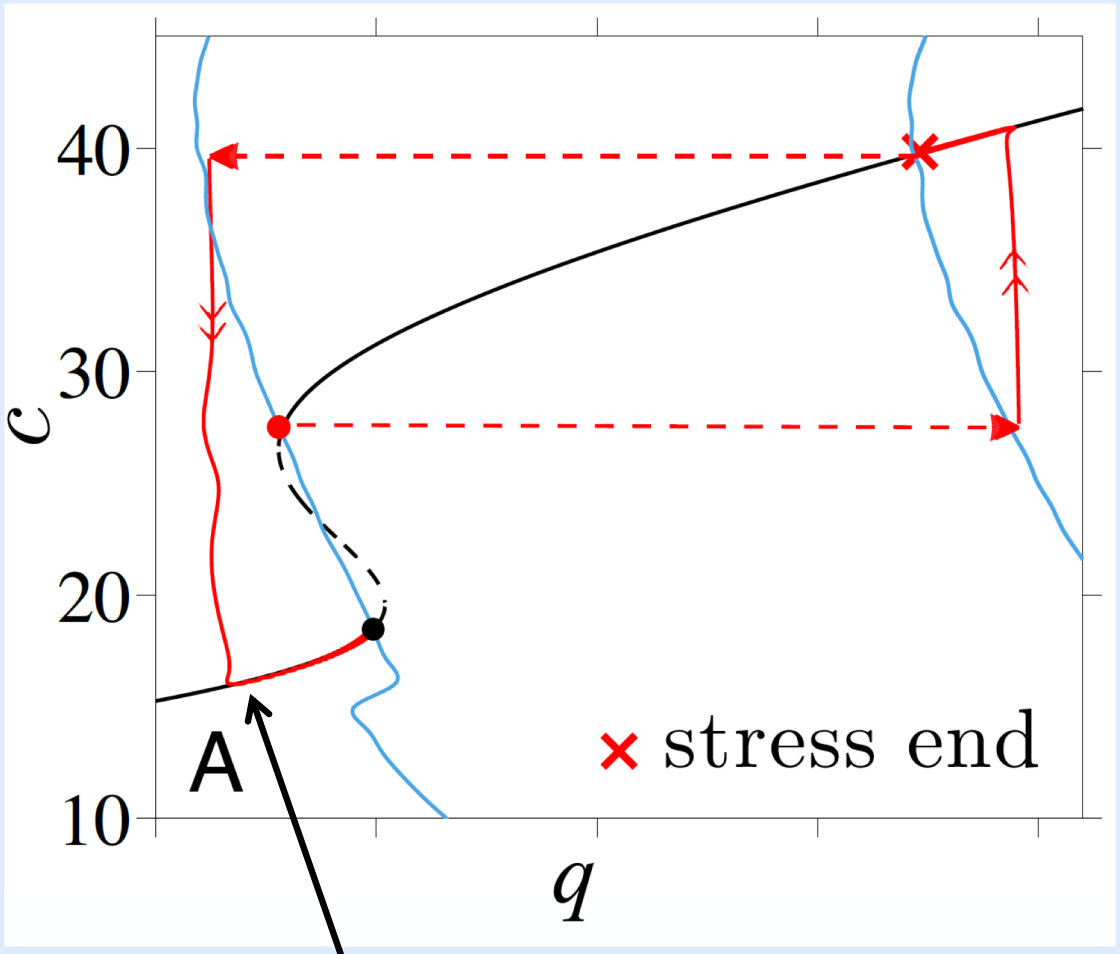
Increase $I_0 \rightarrow I_0 + I_{ext}$



The system will find its new equilibrium at the new nullcline intersection

Let's now turn I_{ext} off

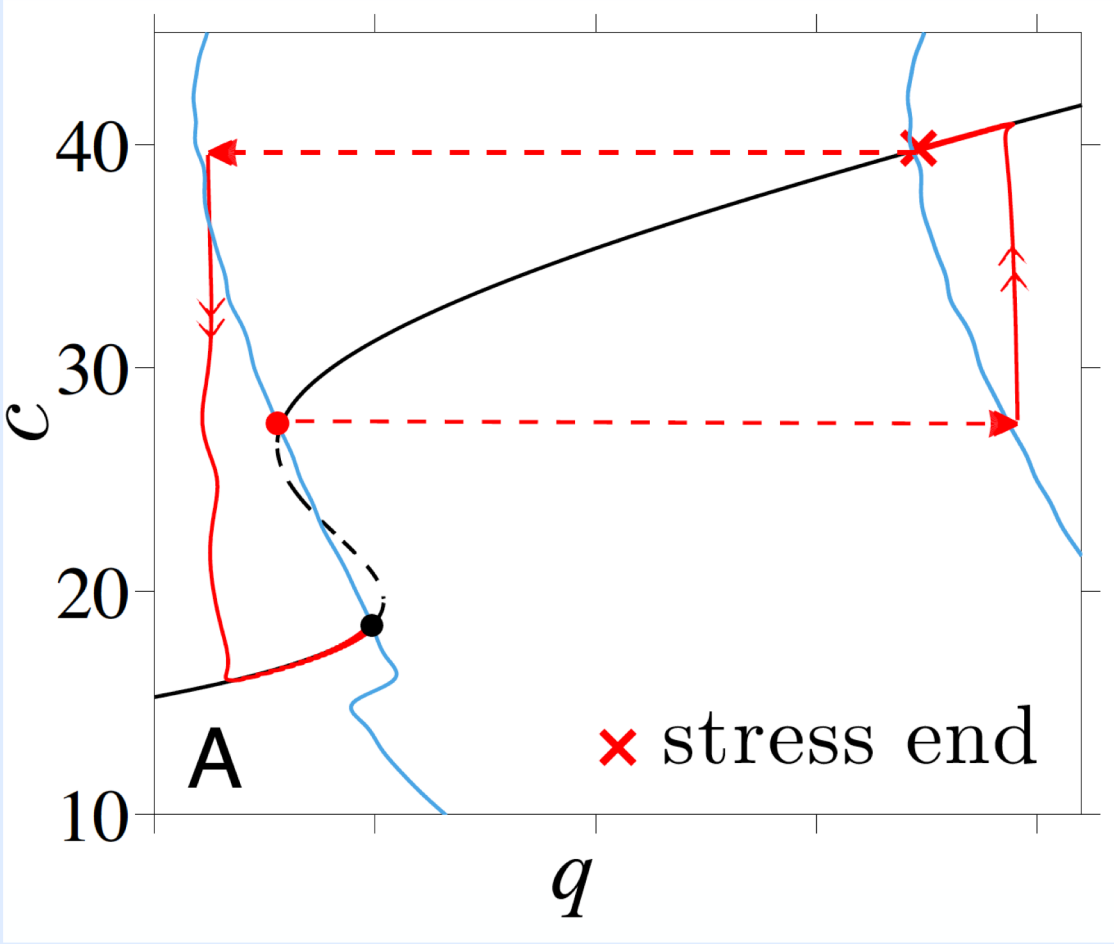
Turn off $I_0 + I_{ext} \rightarrow I_0$



The q nullcline will shift back towards its original location

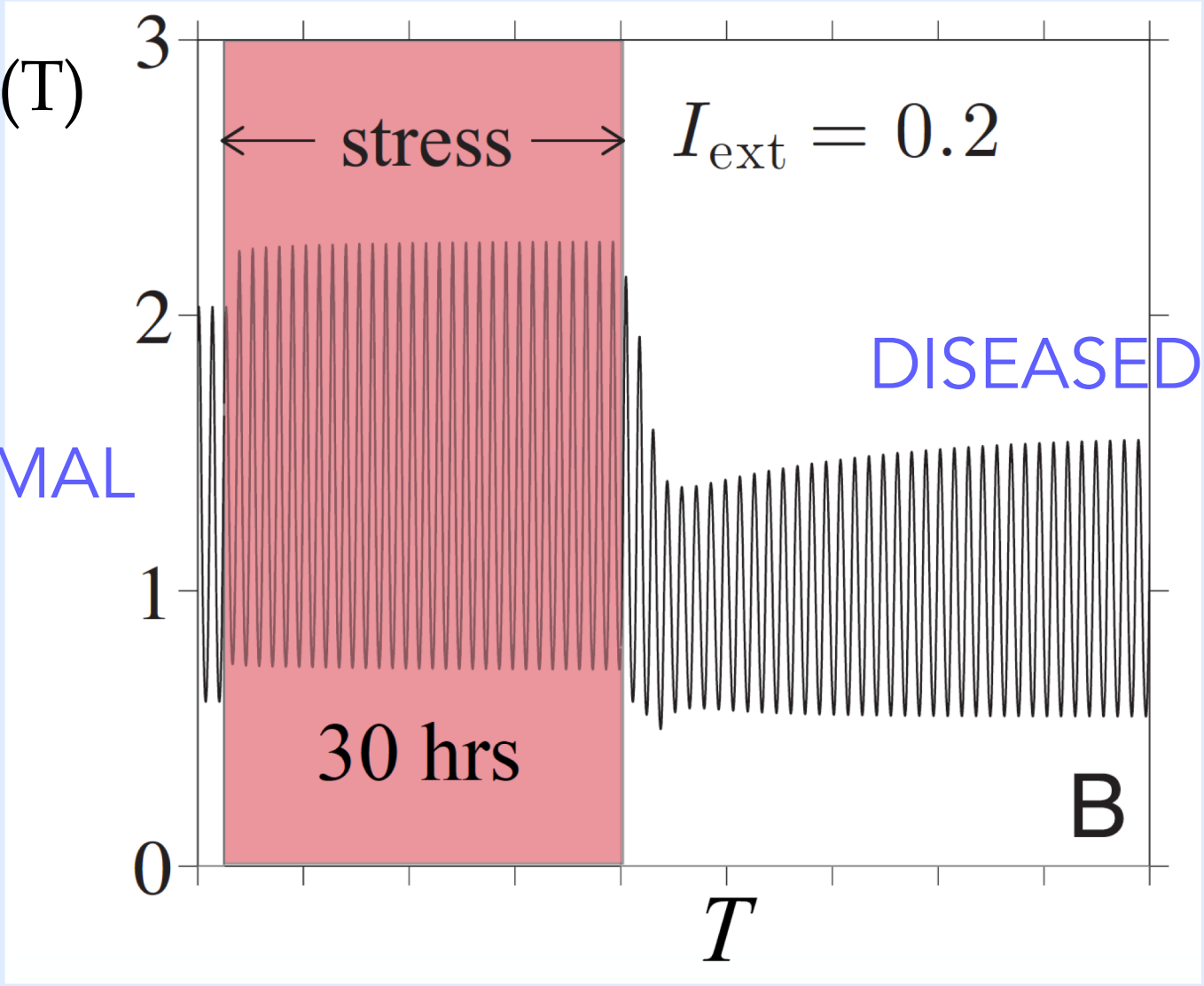
The system will find the fast nullcline first and then move towards the diseased state

A temporary but prolonged I_{ext} ...



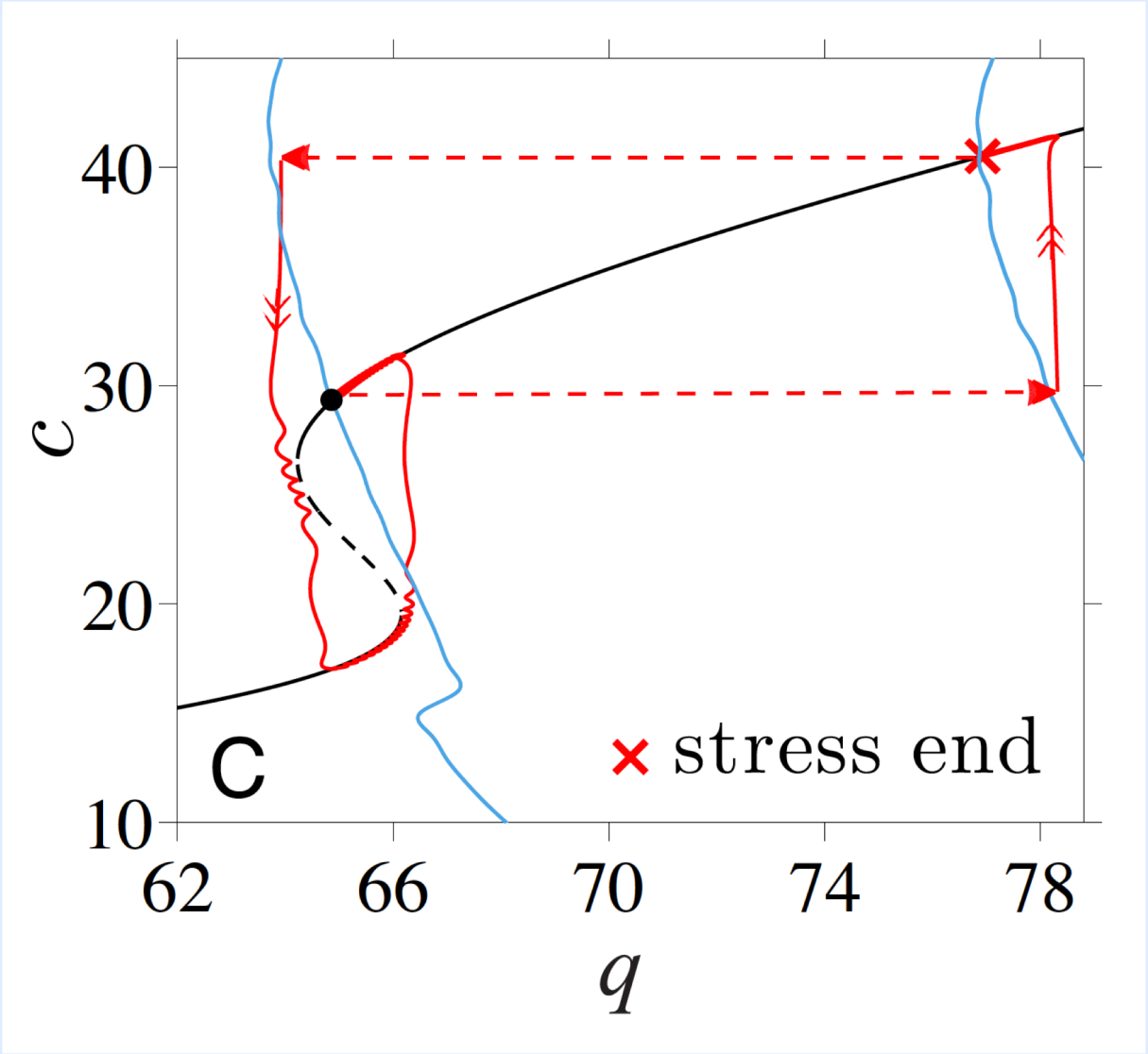
...led us from normal to diseased states
30 hours of external stress

Cortisol for I_{ext} =0.2; stress for 30 hs



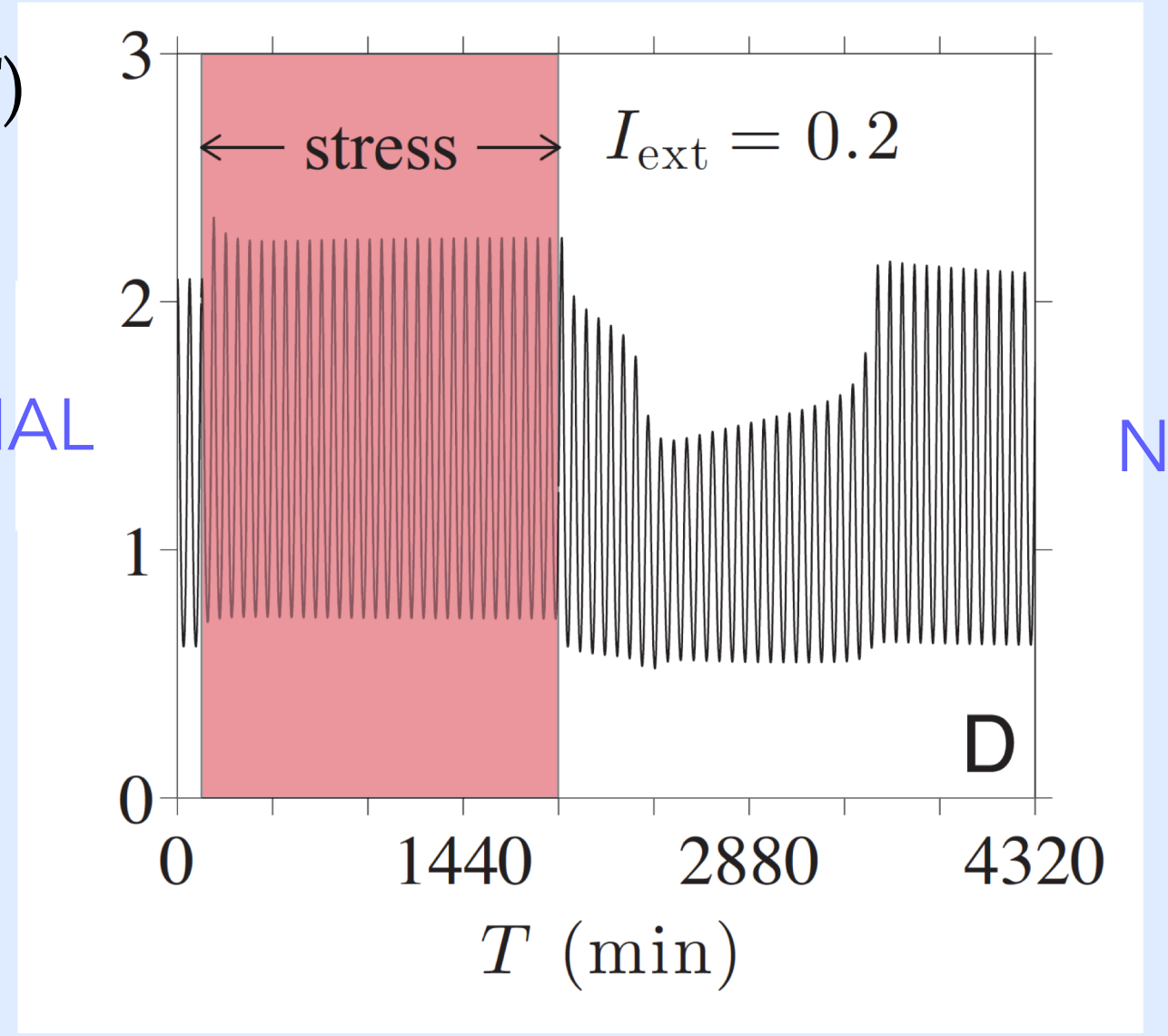
Normal (high cortisol) to diseased (low cortisol)

Resistant case



If there is only one intersection, the system eventually returns to the normal state.

Cortisol for I_{ext} =0.2; stress for 30 hs

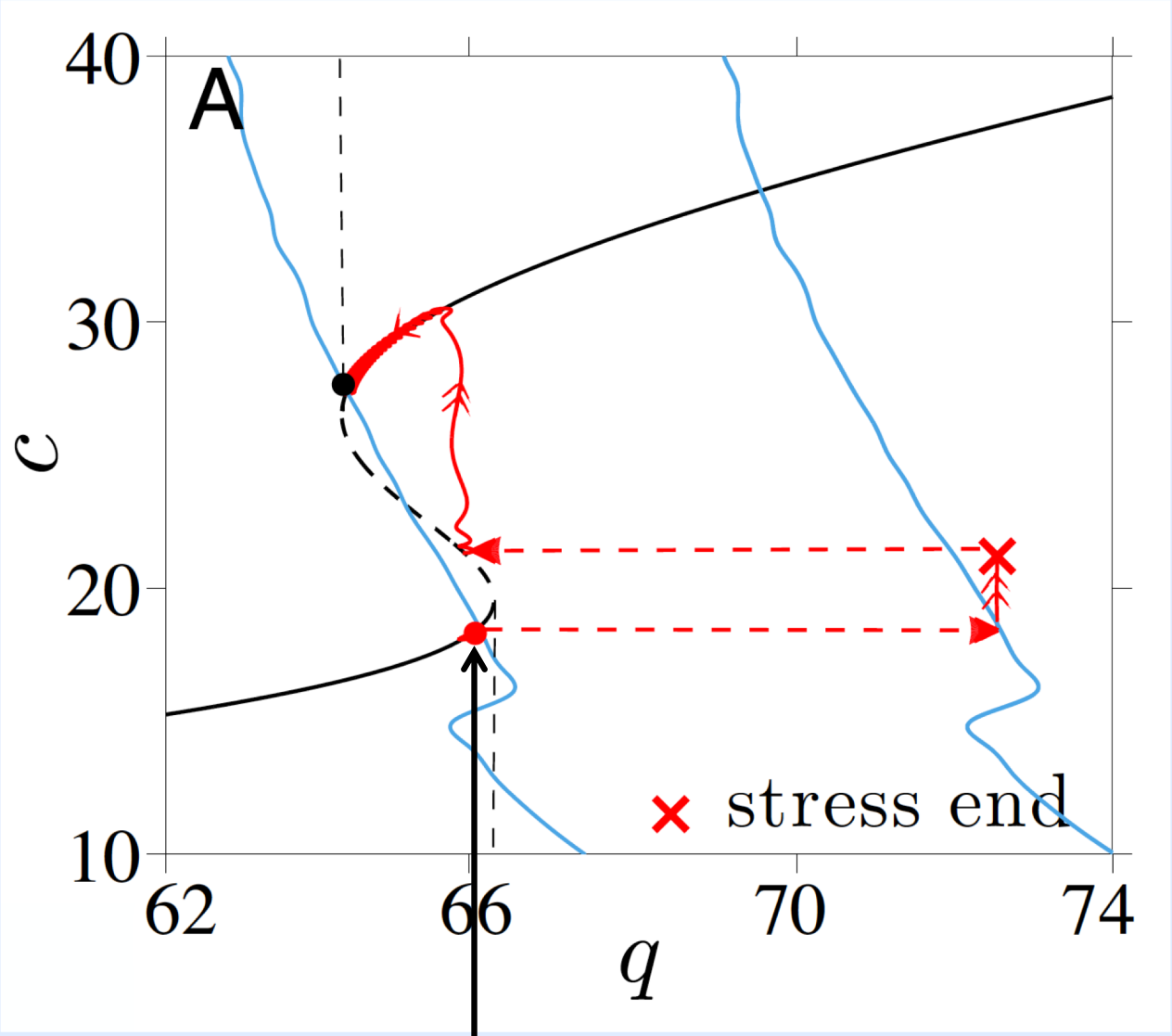


NORMAL

NORMAL

A resistant individual

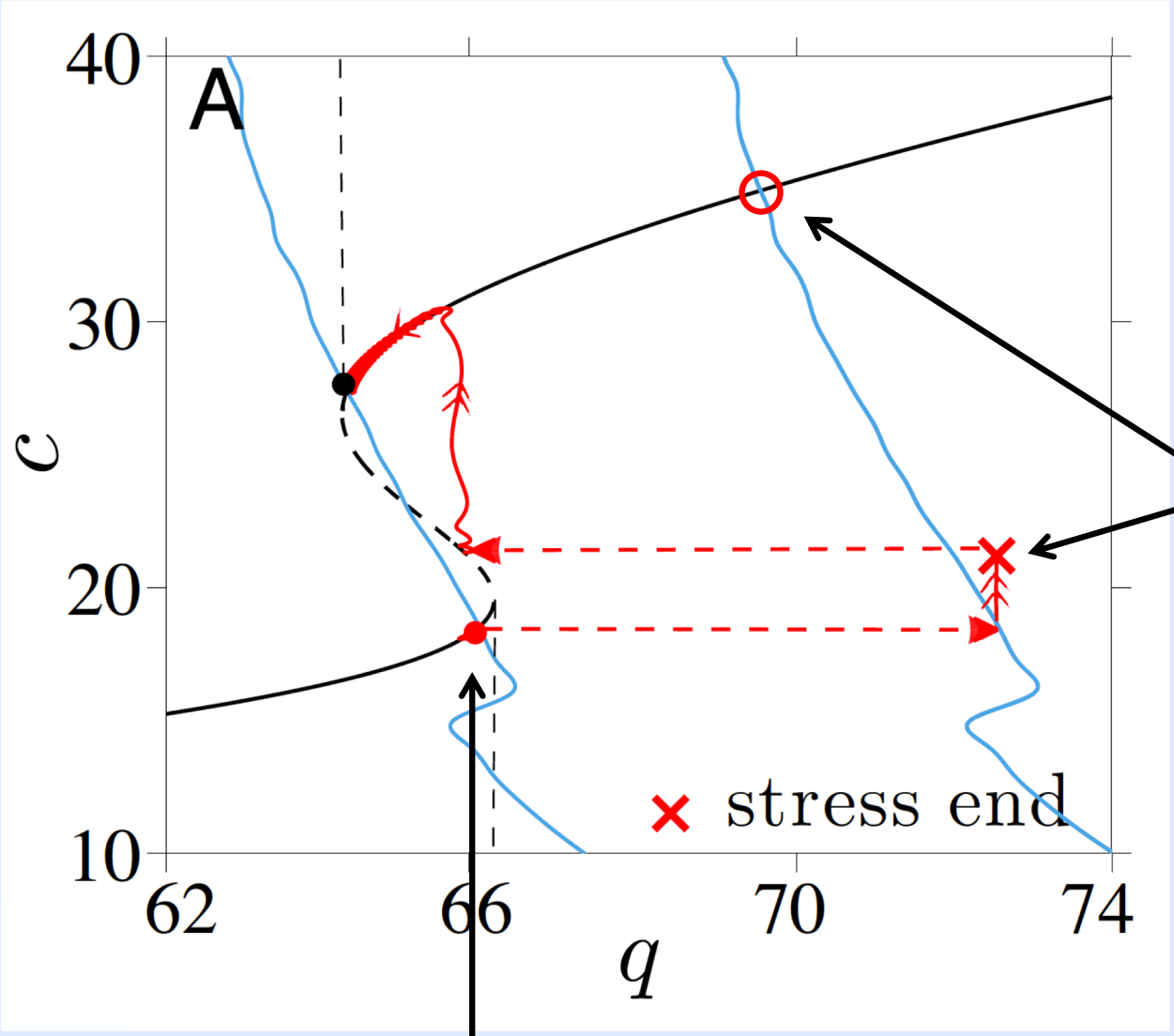
Diseased to Normal?



Diseased state, START turn on I_{ext}

$$q = p_c\,(I+I_{ext})\,h(c_s(c))$$

Increase $I_0 \rightarrow I_0 + I_{ext}$ (short time)

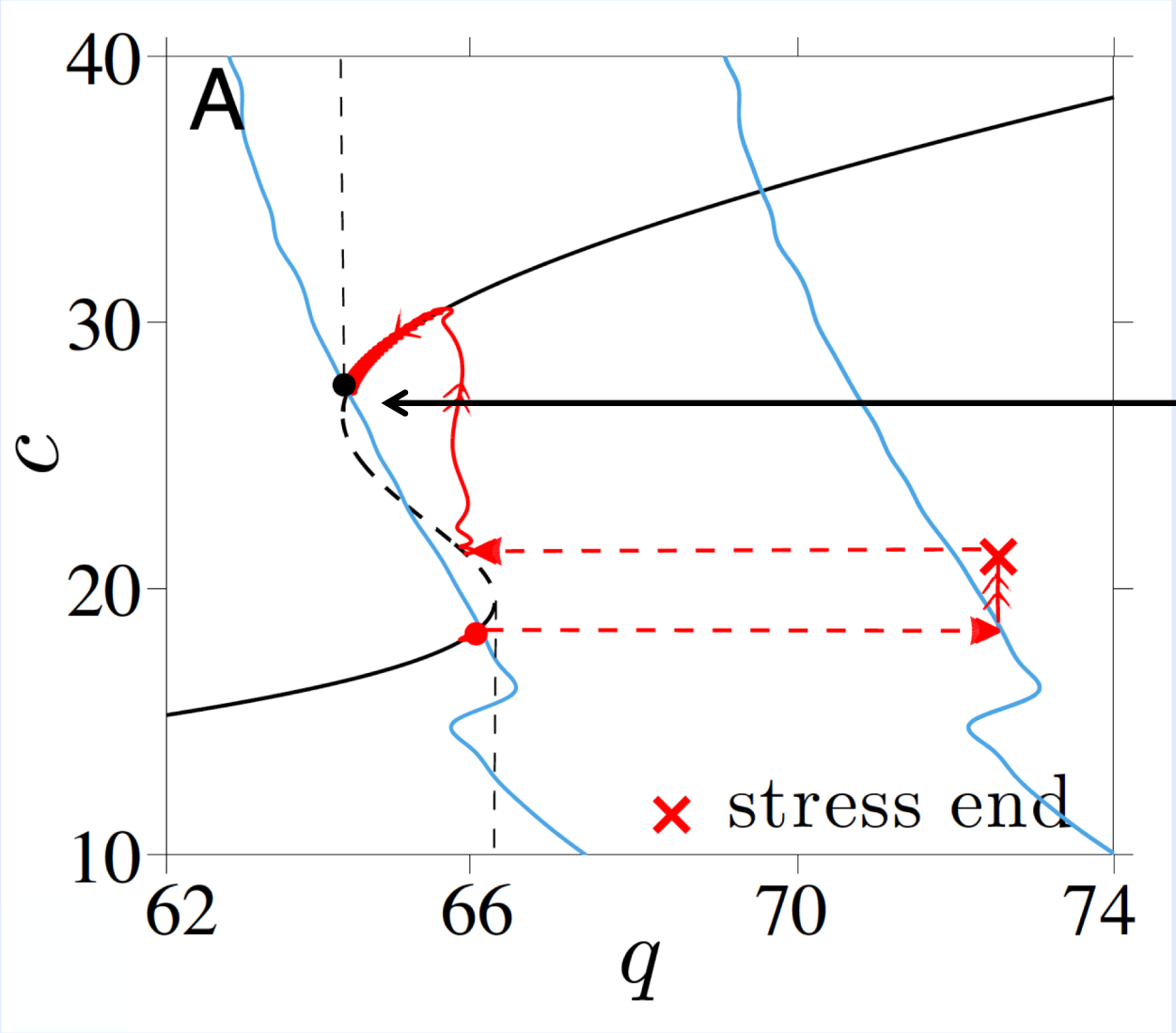


q increases

We turn off stress before the system can reach the new equilibrium

Diseased state, START
turn on I_{ext}

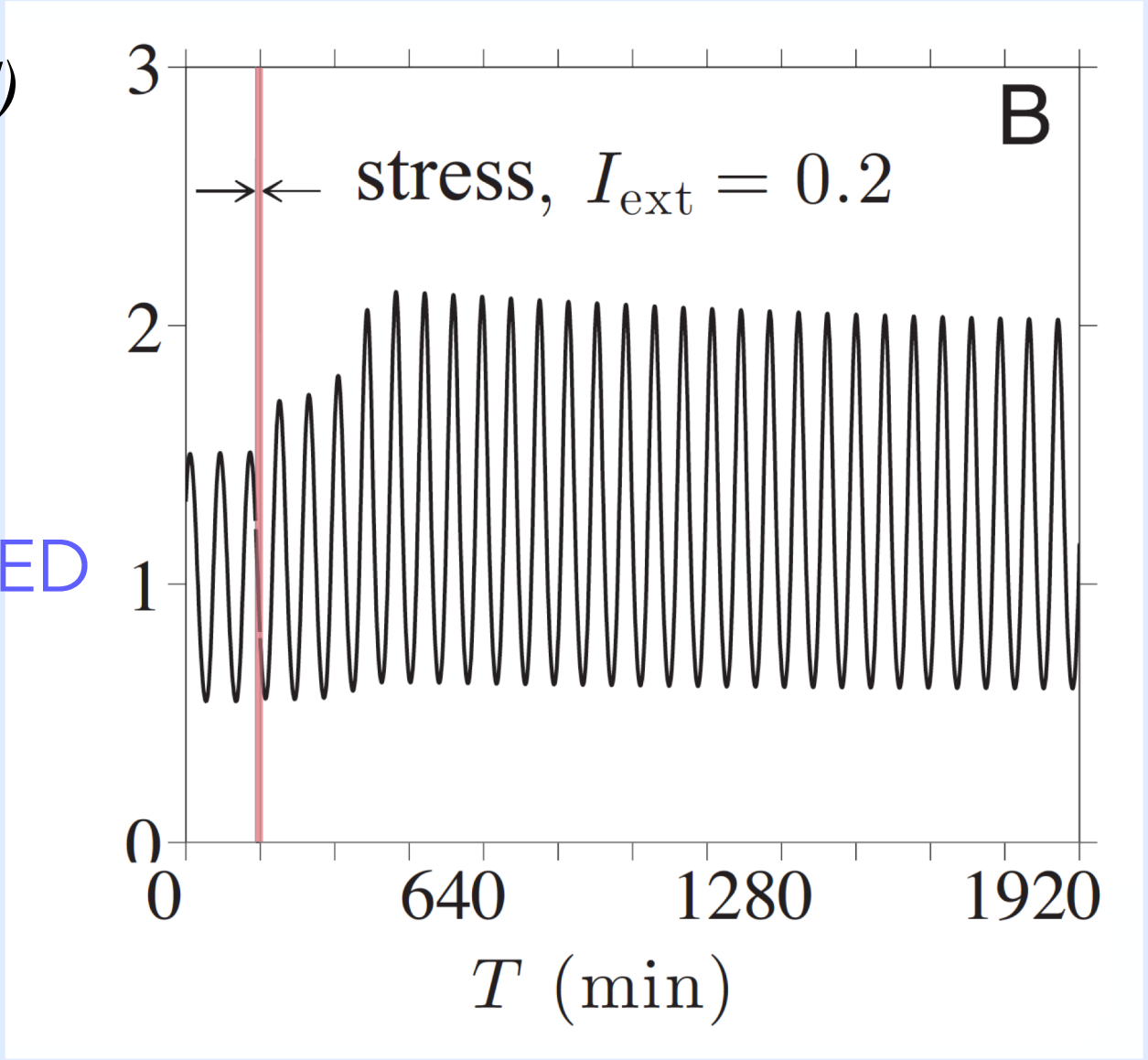
Turn off $I_0 + I_{ext} \rightarrow I_0$



The system will relax back to the fast nullcline first and finally to the normal state

Short time stress can lead to a reverse transition!

Diseased to Normal

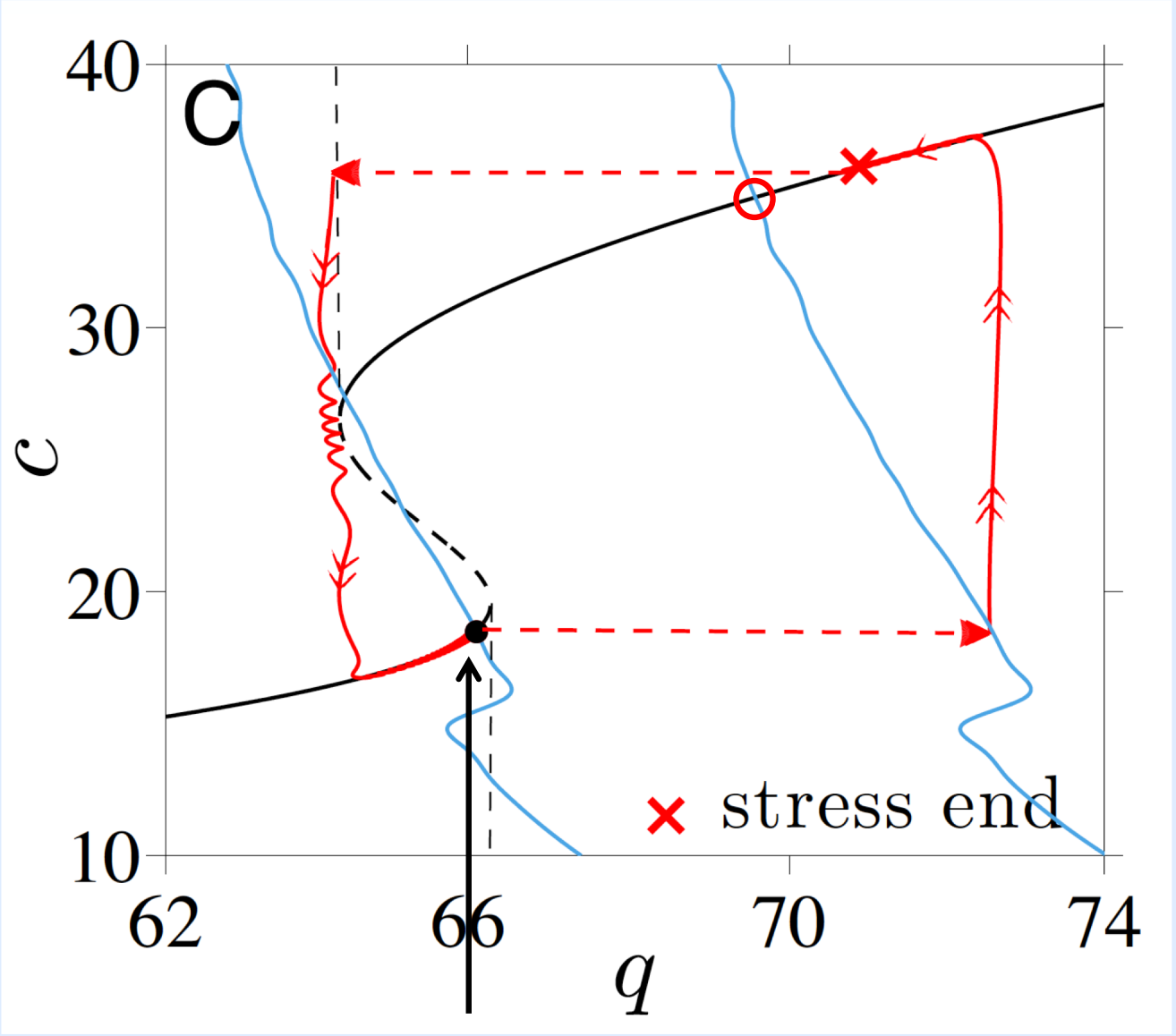


DISEASED

NORMAL

Short time external stress can reverse transition!

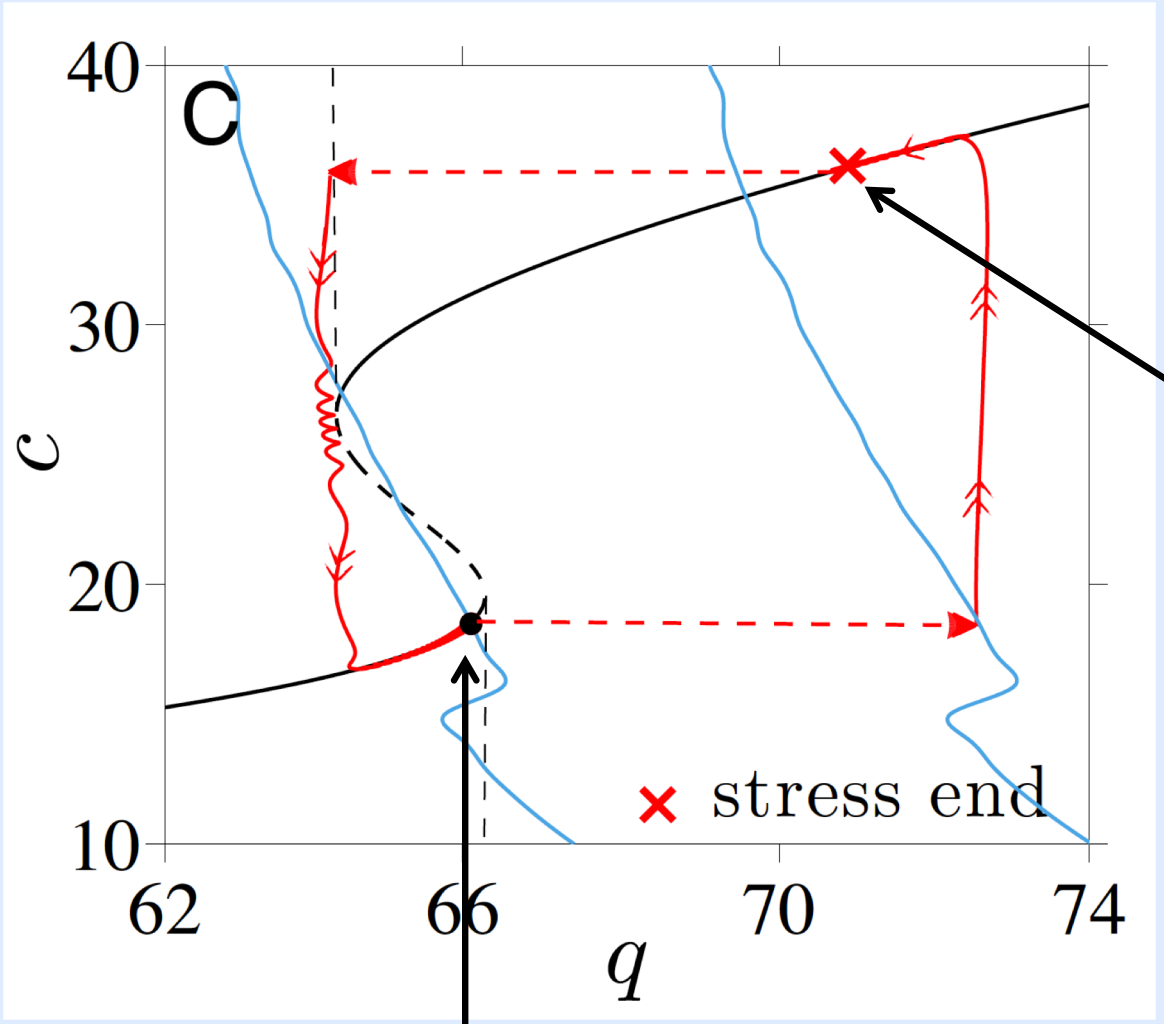
Diseased to Normal?



Diseased state, START turn on I_{ext}

$$q = p_c\,(I+I_{ext})\,h(c_s)$$

Increase $I_0 \rightarrow I_0 + I_{ext}$ (long time)



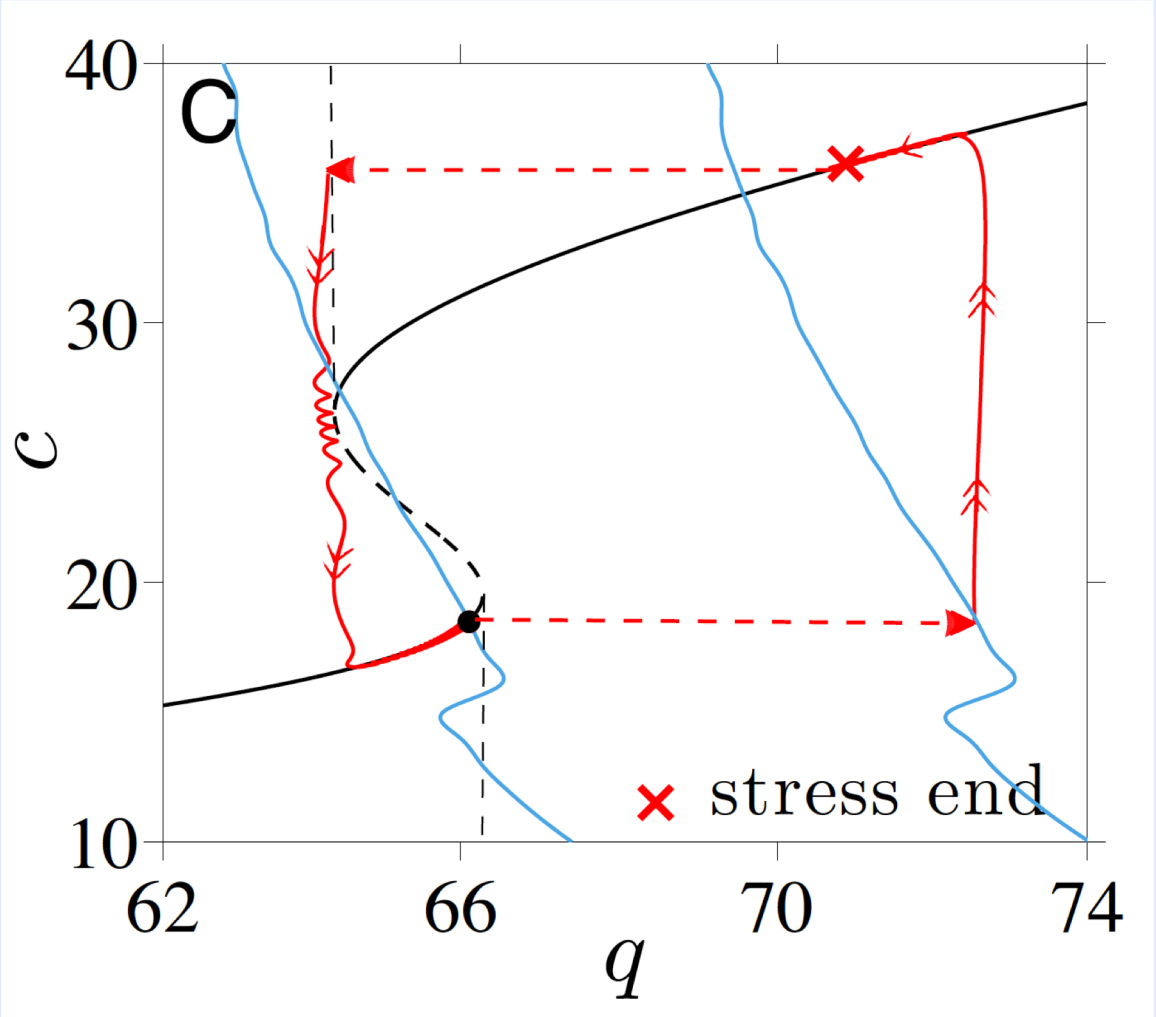
q increases

We turn off stress almost at the new equilibrium

Diseased state, START

turn on I_{ext}

Turn off $I_0 + I_{ext} \rightarrow I_0$



q decreases

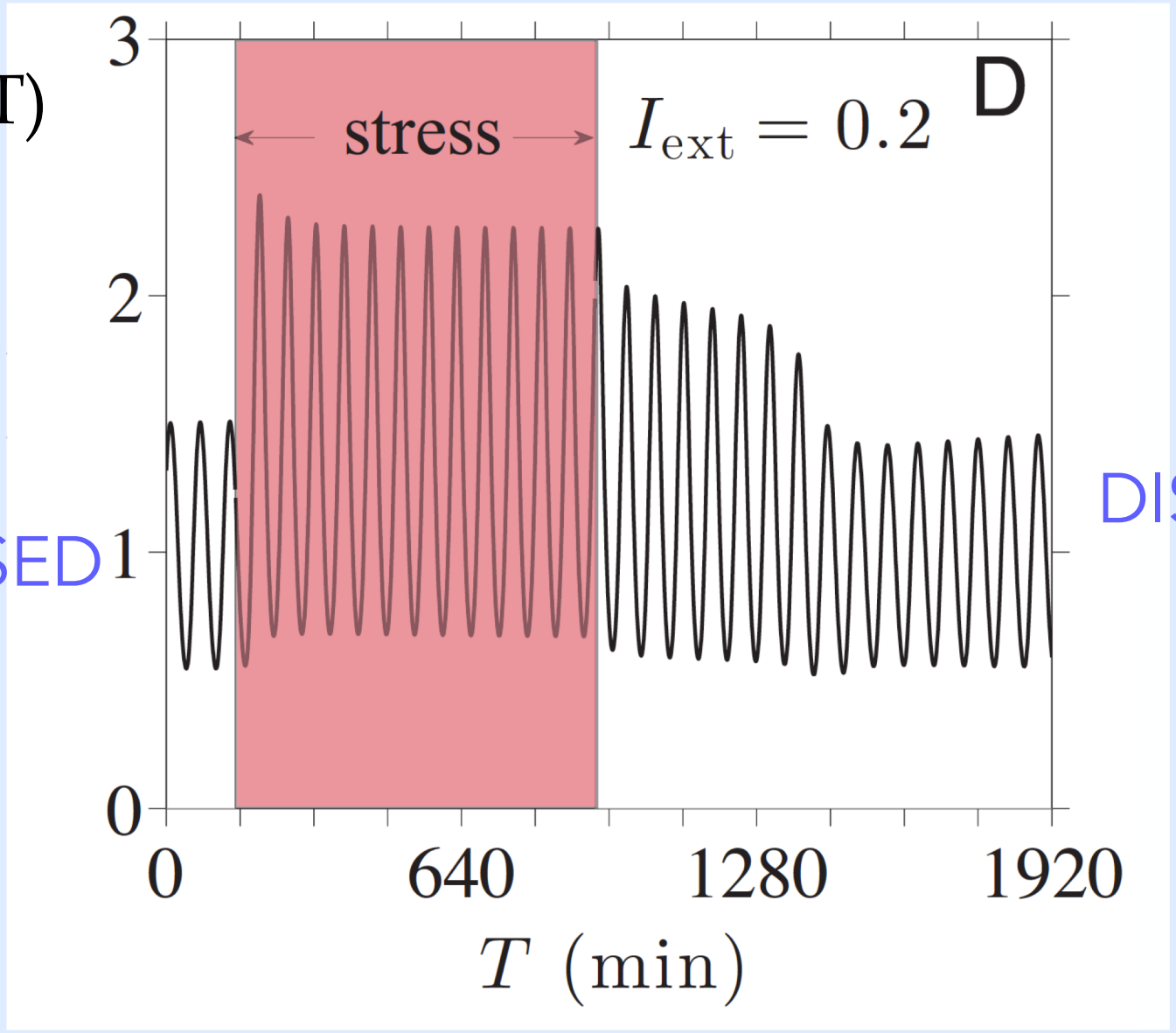
Not able to find the normal state

The fast nullcline is reached

Relax back to the diseased state

Long time external stress does not allow for a transition

Diseased to Diseased



DISEASED

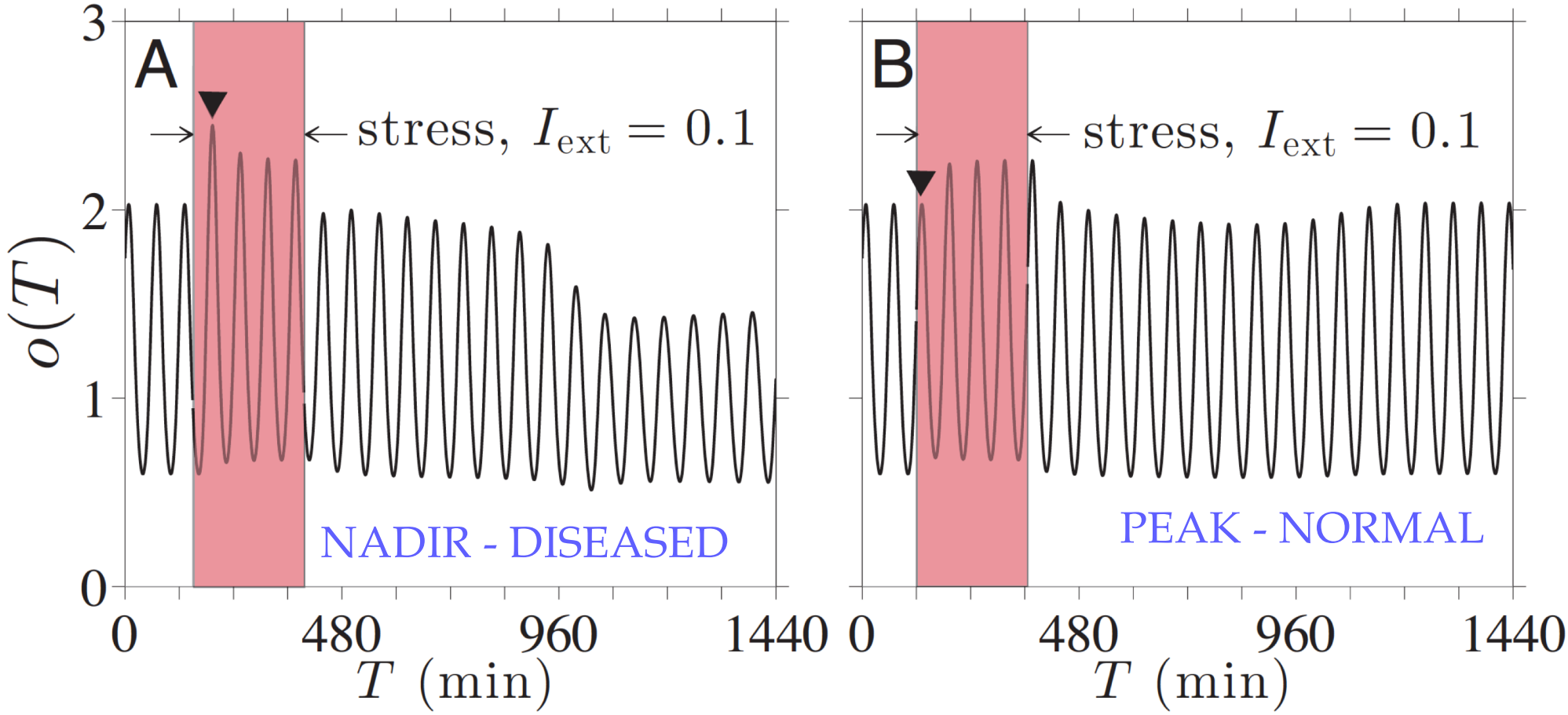
DISEASED

No permanent transition

Can induce transitions
between normal and diseased states and
vice-versa depending on magnitude and
duration of stress

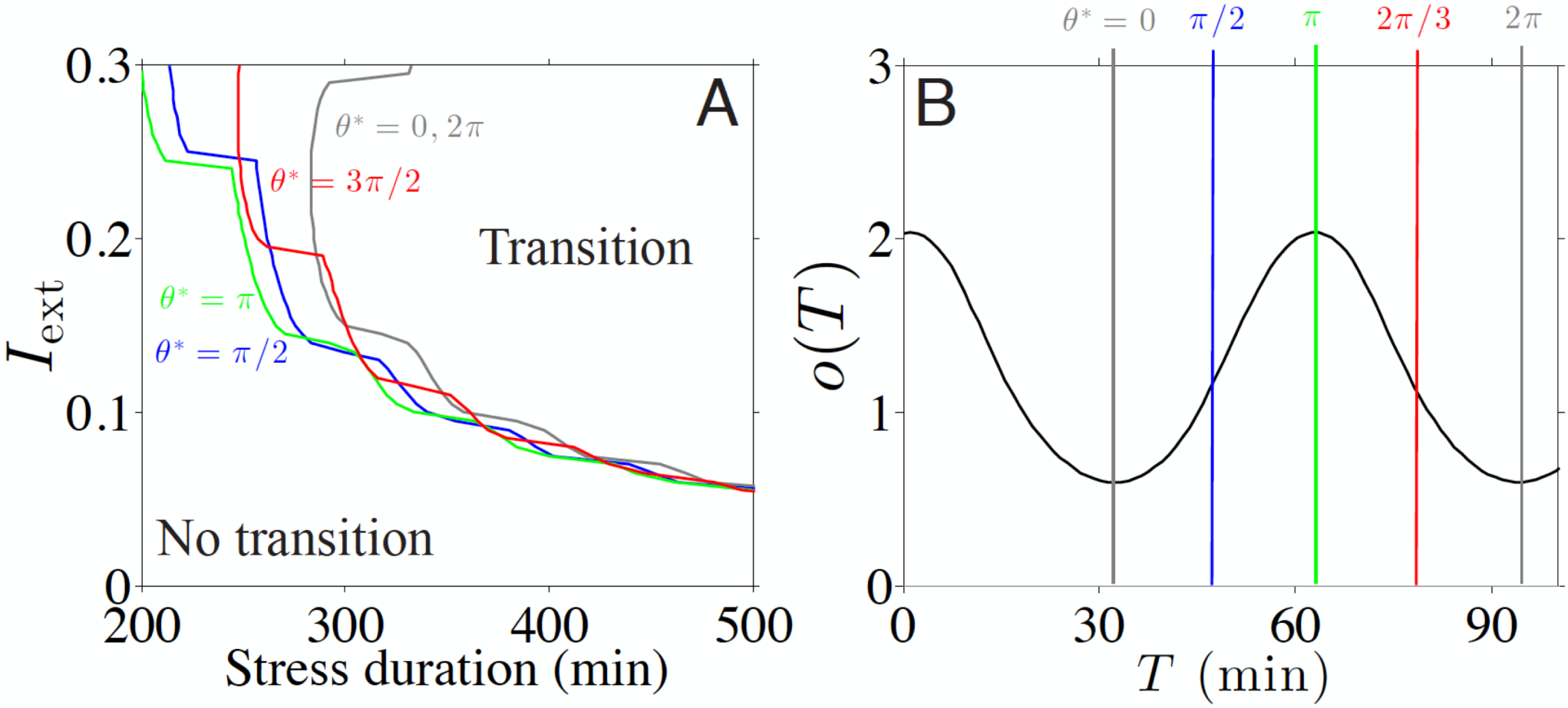
w/o changing physiological parameters

Timing of stressor?



External stress: same 0.1 magnitude, 250 min duration, but different phases of cortisol oscillation

Normal to diseased transition



Higher intensity – Shorter duration
Phase at onset dependence
At peak transition more likely

Conclusions

Introduced a bistable dynamical model
Physiologically motivated feedback
Normal and diseased (oscillating) states

Stress-induced normal-diseased, reversible transitions

No physiological parameter changes

Transitions depend on magnitude, duration, timing of stress

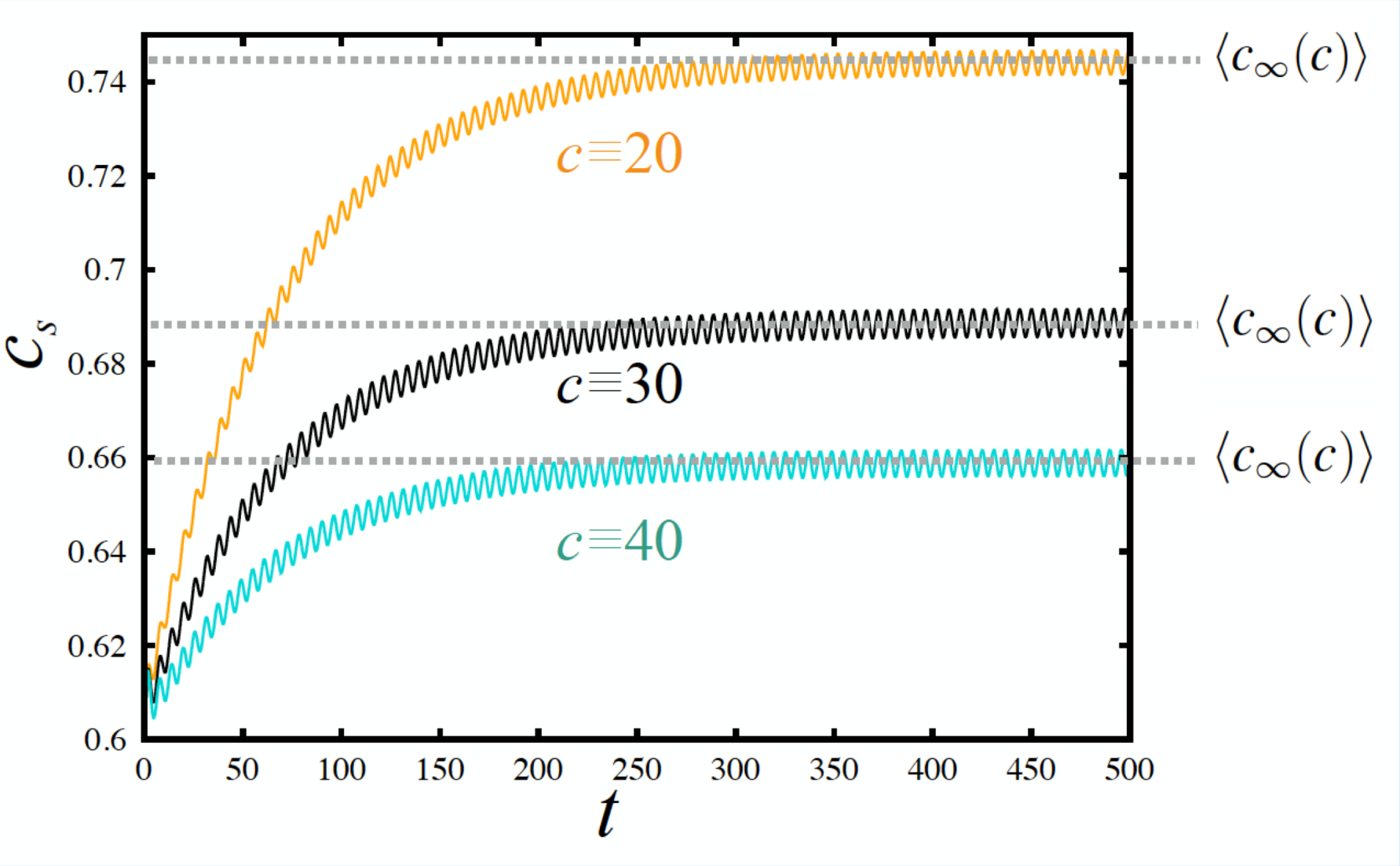
Circadian Clock? Higher brain? I(t)? Experiments?

Thanks:

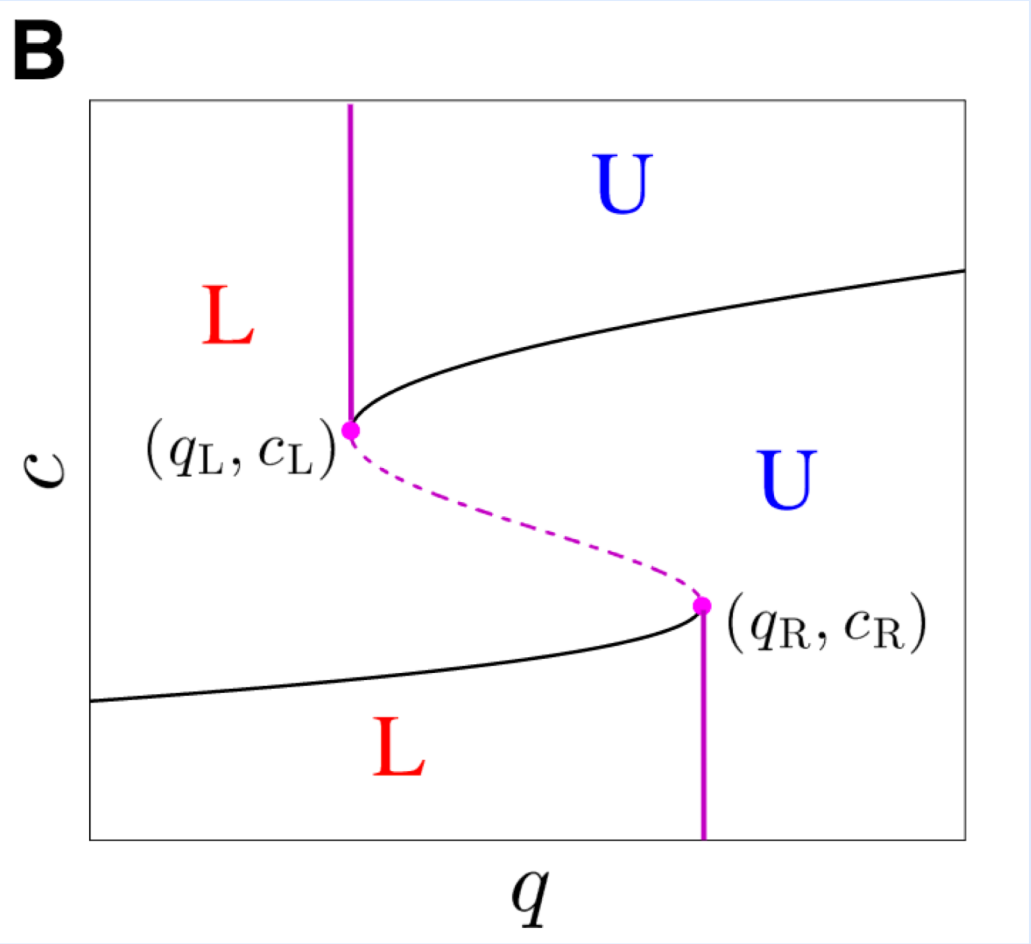
L. Kim, T. Chou, A. Singh, Y. L. Chuang (UCLA)

T. Minor and M. Wechselberger (UCLA)

Closing


0.74
0.72
0.7
0.68
0.66
0.64
0.62
0.6
c_s
0
50
100
150
200
250
300
350
400
450
500
t
$c \equiv 20$
$c \equiv 30$
$c \equiv 40$
$\langle c_\infty(c) \rangle$
$\langle c_\infty(c) \rangle$
$\langle c_\infty(c) \rangle$

Recall



The separatrix lines determine basins of attraction

L – lower

U - upper

Non dimensionalization

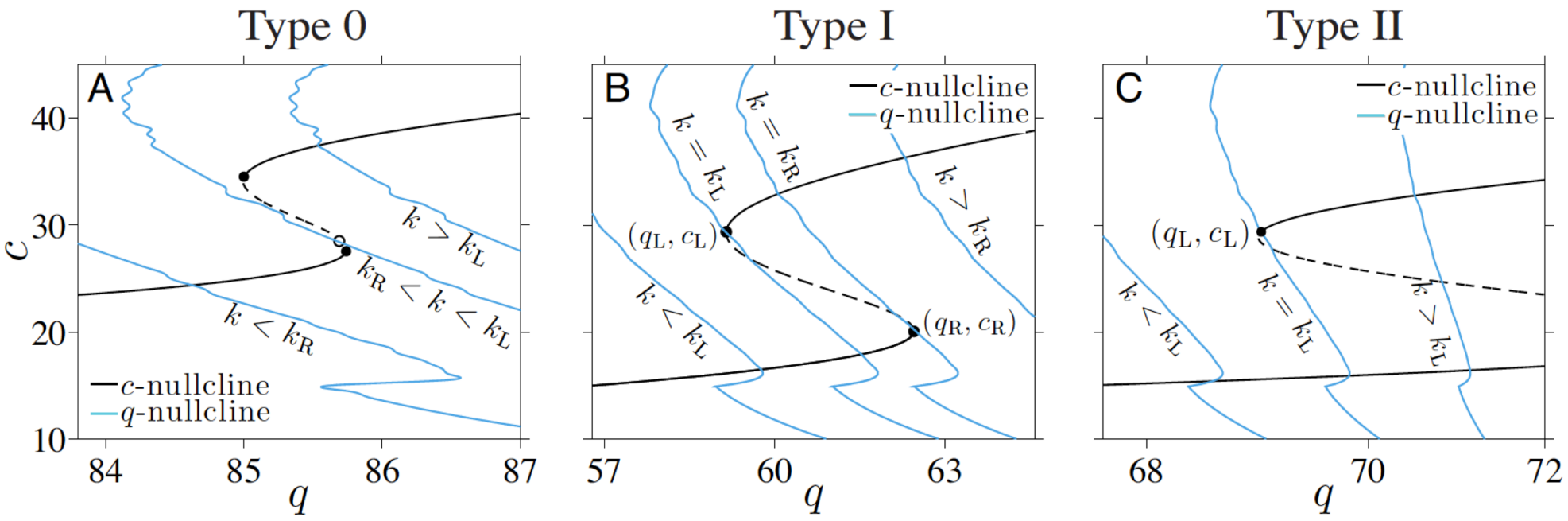
Our equations are nondimensionalized in a manner similar to that used by Walker *et al.* [13]:

$$
\begin{aligned}
t &= d_O T, & c_\mathrm{s} &= C_\mathrm{s}/\bar{C}_\mathrm{s}, & c &= \mu_R p_C d_O C, \\
a &= \mu_R p_C d_O^2 A, & r &= \mu_R p_C d_O R, & o &= \mu_R p_C p_A p_O d_O^3 O,
\end{aligned} \tag{A1}
$$

Here, c_s, c, a, r, o are the dimensionless versions of the original concentrations C_s, C, A, R, O, respectively. C_s is normalized by $\bar{C}_\mathrm{s}$, which denotes the typical maximum amount of releasable CRH in the physiological range. Upon using these variables, the dimensionless forms of Eqs. 8-12 are expressed in Eqs. 13-17. The parameters q_i, p_i are dimensionless combinations conveniently defined to be analogous to those used by Walker *et al.* [13]:

$$
\begin{aligned}
t_c &= d_O T_C, & t_\mathrm{d} &= d_O T_\mathrm{d}, & q_0 &= p_C/(\mu_R p_R), \\
q_2 &= d_C/d_O, & p_2 &= \mu_R^2 p_R^2 p_A p_O/(d_O^4 K_A), & p_3 &= d_A/d_O, \\
p_4 &= p_C^4 p_A p_O d_O^8 K_R^2/\mu_R, & p_5 &= 1/\mu_R, & p_6 &= d_R/d_O.
\end{aligned} \tag{A2}
$$

Changing k


Type 0
A
40
30
20
10
c
84
85
86
87
q
$k > k_L$
$k_R < k < k_L$
$k < k_R$
c-nullcline
q-nullcline
Type I
B
$k = k_L$
$k = k_R$
$k > k_R$
$k < k_L$
(q_L, c_L)
(q_R, c_R)
57
60
63
q
Type II
C
68
70
72
q

Include slow subsystem

We will only look at $(q(c_s),\ c)$
all other variables can be determined via the PA subsystem for a given c

$$\frac{dc_s}{dt} = \frac{c_\infty(o) - c_s}{t_c}$$

$t_c \rightarrow \infty \qquad c_s \rightarrow c_\infty(o)$ or $c_\infty(o(c))$

$q(c_s) = p_c\, I(t)\, h(c_s)$, use $I(t) = I_0$

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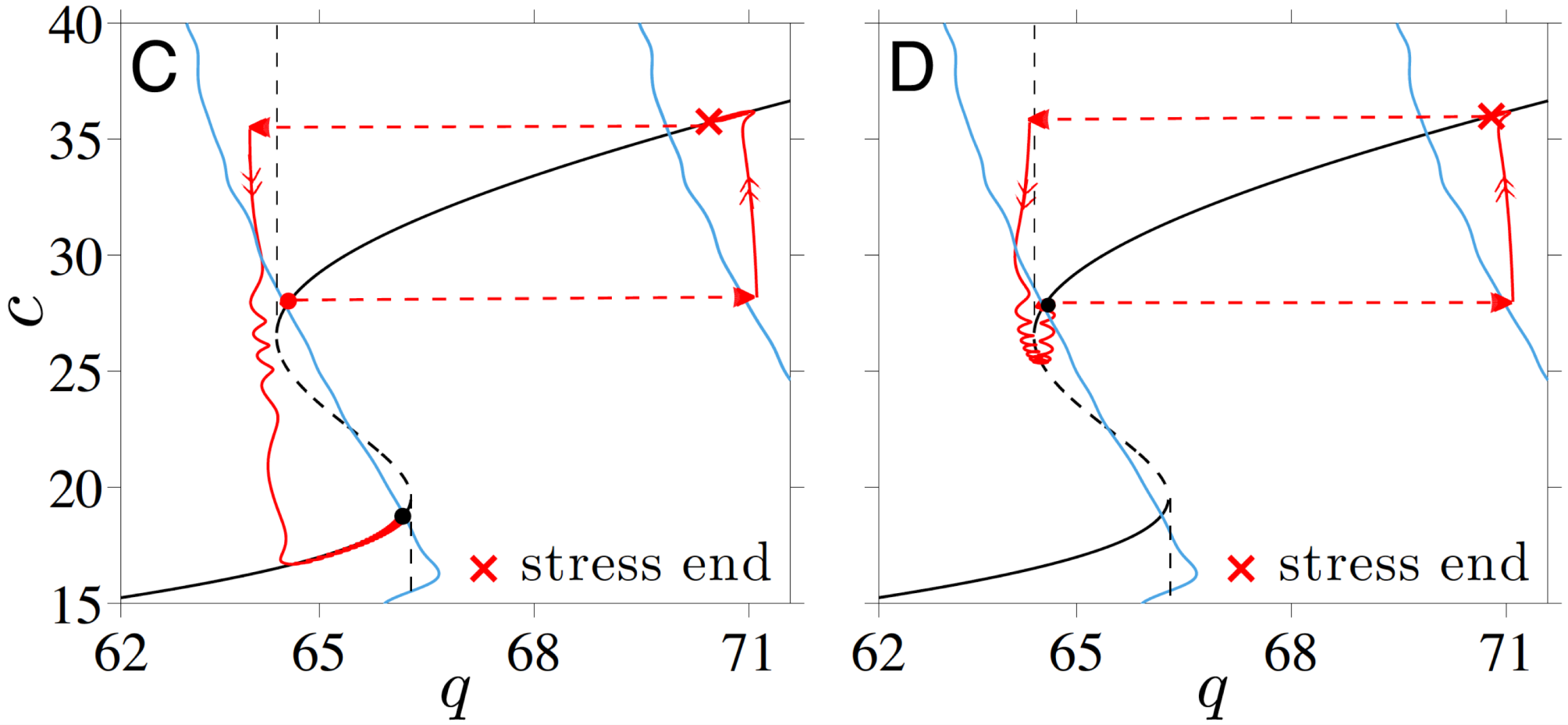
$q(c_s) \rightarrow q(c_\infty(o))$ or $q(c_\infty(o(c)))$

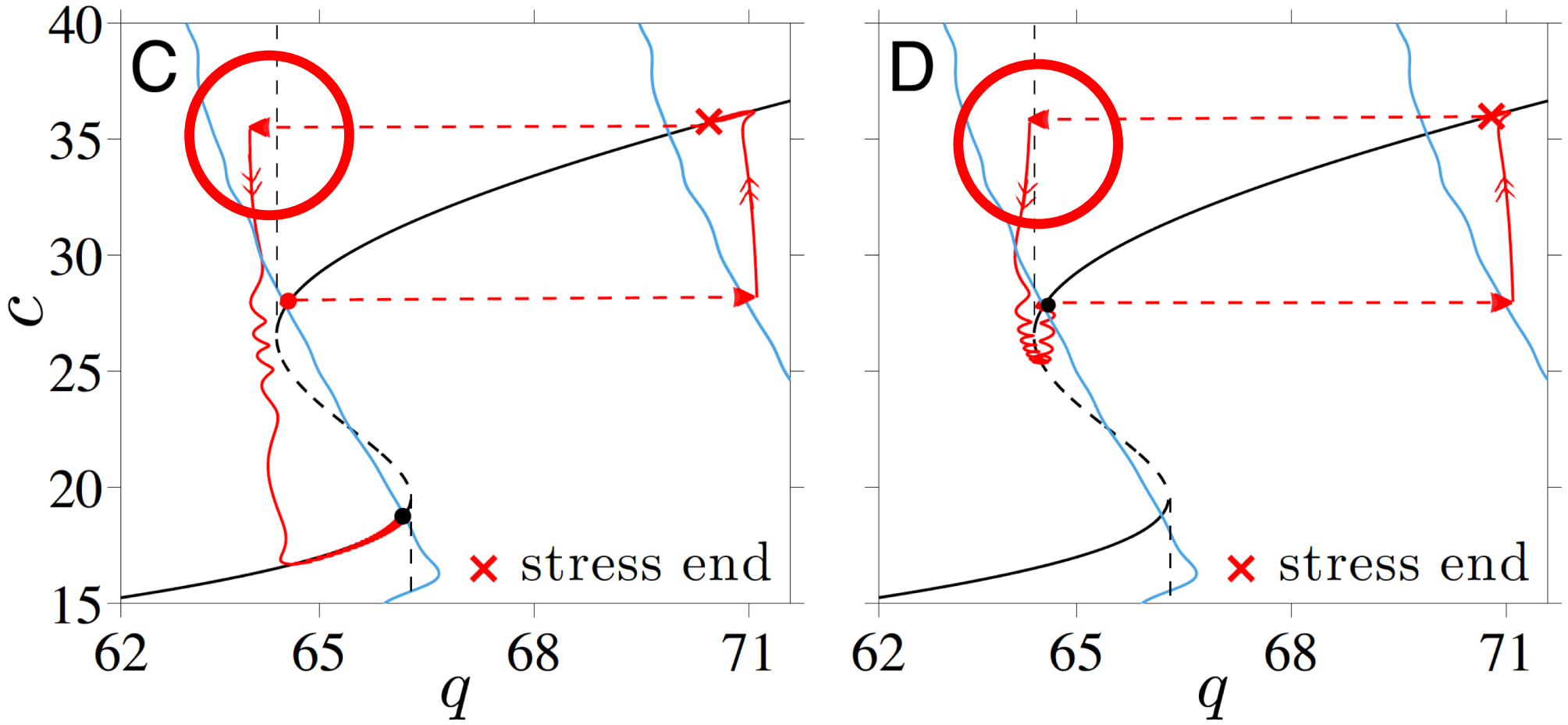
Have a function $q(c)$ as slow q nullcline ; use $\overline{o}$

Timing of stressor?



Timing of stress onset determines position of the state relative to the separatrix at stress end

Timing of stressor?



Timing of stress onset determines position of the state relative to the separatrix at stress end