이론물리학자의 인공 췌장 도전기:

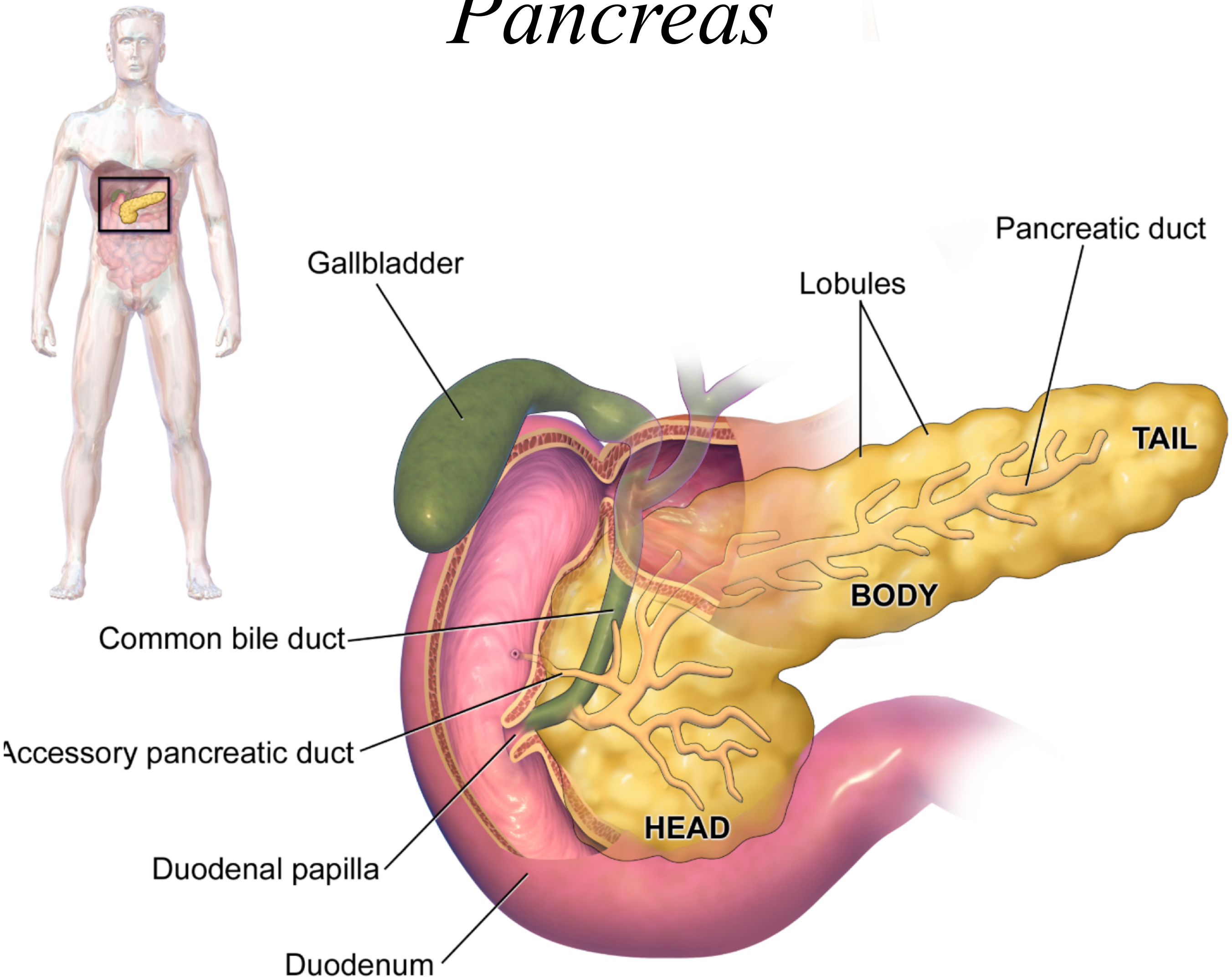
도전을 시작하며

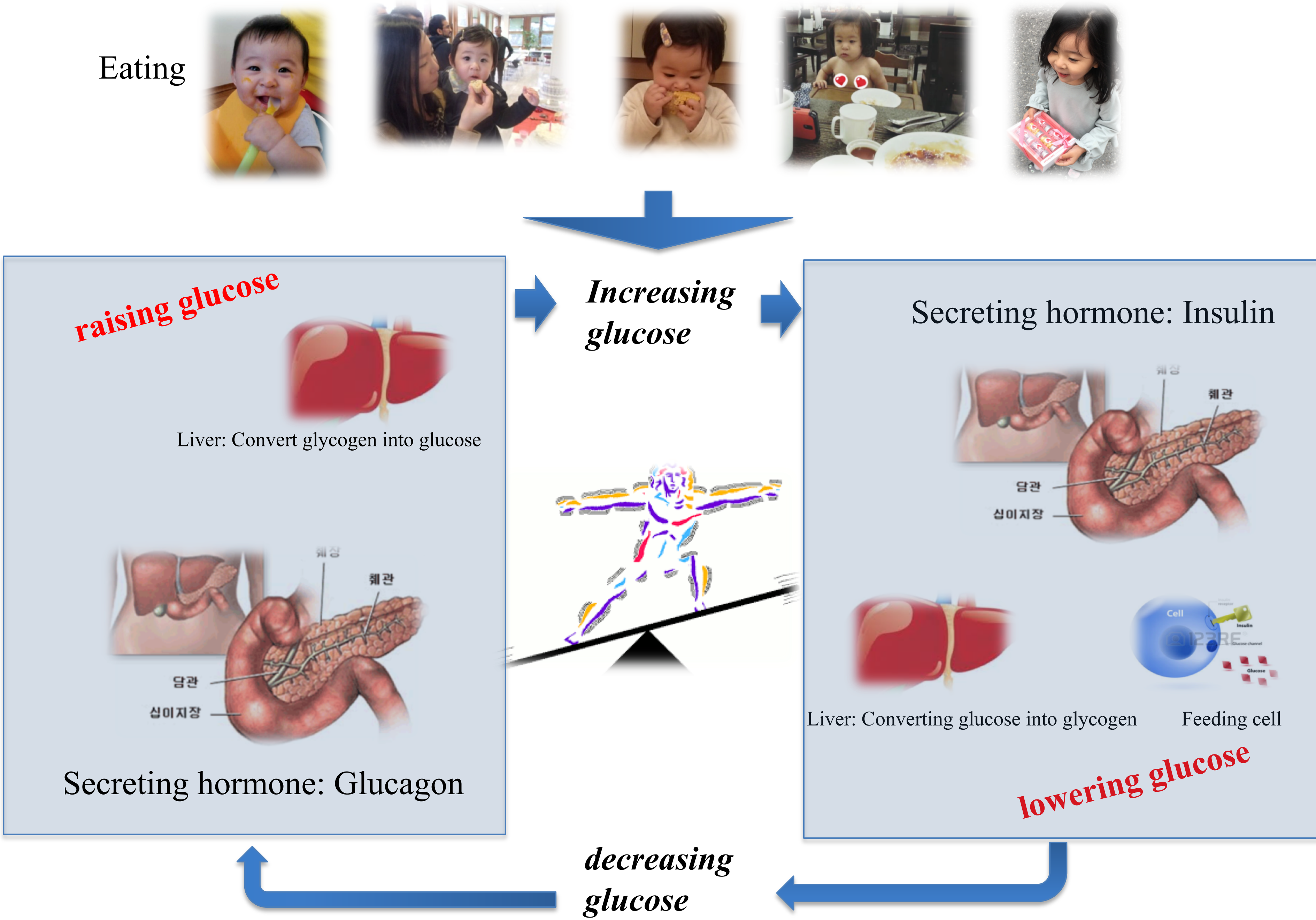
송태근

포항공대 물리학과 연구교수

2019 생명 물리 여름학교

Pancreas


Gallbladder
Pancreatic duct
Lobules
TAIL
BODY
Common bile duct
Accessory pancreatic duct
HEAD
Duodenal papilla
Duodenum


Eating
Increasing glucose
raising glucose
Liver: Convert glycogen into glucose
췌장
췌관
담관
십이지장
Secreting hormone: Glucagon
Secreting hormone: Insulin
췌장
췌관
담관
십이지장
Cell
Liver: Converting glucose into glycogen
Feeding cell
lowering glucose
decreasing glucose

ὅμοιος[*homoios*], "similar"

\+
στάσις[*stasis*], "standing still"

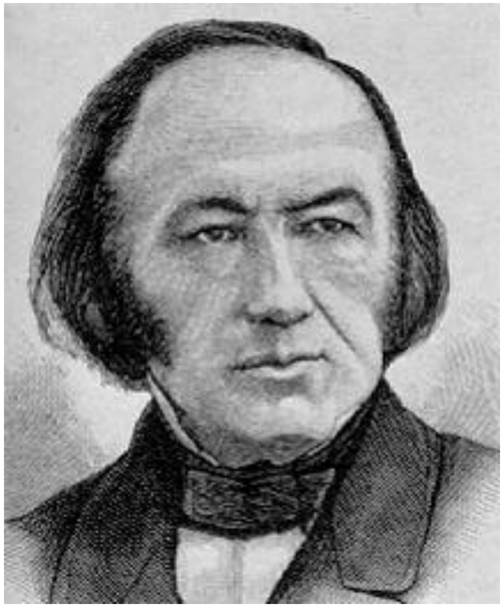
= "staying the same"

...생명, 자연, 환경 – 거기에 살아 숨쉬는 모든 현상의 핵심을 풀수 있는 키워드,
나는 그것을 '동적평형'이라 생각한다...

후쿠오카 신이치저 '동적평형'

Endocrine system

Claude Bernard: the father of endocrinology



Claude Bernard stated that the endocrine system regulates the internal milieu of an animal.

The "internal secretions" were liberated by one part of the body, traveled via the bloodstream to distant targets cells.

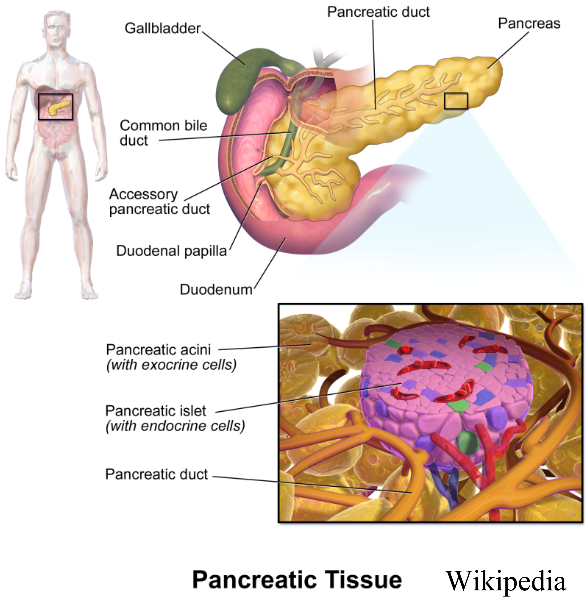
- ➢ The concept that hormones acting on distant target cells to maintain the stability of the internal milieu was a major advance in physiological understanding.

- ➢ The secretion of the hormone was evoked by a change in the milieu and the resulting action on the target cell restored the milieu to normal.

The desired return to the status results in the maintenance of **homeostasis**

Pancreatic islets (endocrine system in pancreas)

- Regions of the pancreas that contain three types of endocrine cells.
- Discovered in 1869 by German pathological anatomist Paul Langerhans.
- 3 million islets distributed in the pancreas of a healthy adult human.
- The islet measures an average of about 0.1 mm (109 μm) in diameter.
- Islets are physically isolated and secrete hormones directly into blood flow
- Hormones are secreted with a pulsatile manner

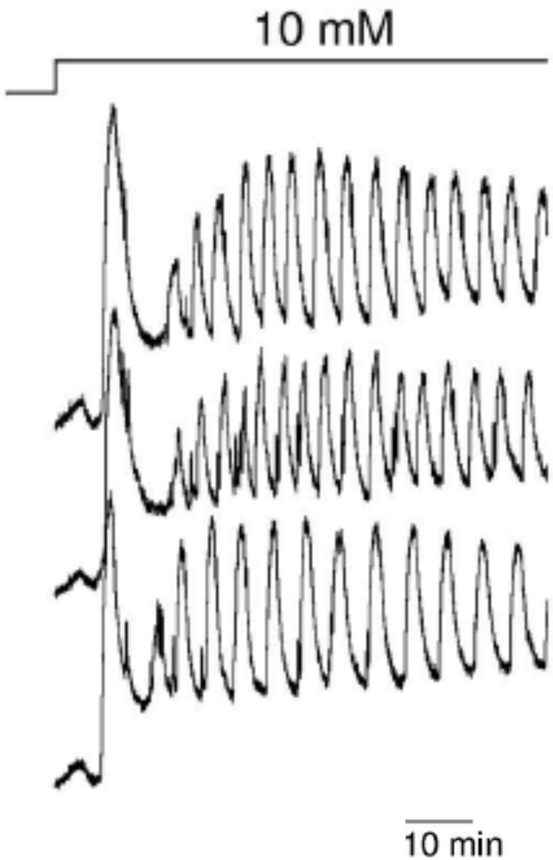


Wikipedia

Endocrine cells

α cell	**Glucagon**	**20 ～ 30 %**	**Increasing glucose**
β cell	**Insulin**	**60 ～ 70 %**	**Decreasing glucose**
δ cell	**Somatostatin**	**～10 %**	**Controlling activity of α and β cell**

Composition is different depending on species



Model for single β-cell

$$\tau \frac{dV_i}{dt} = -I_{iCa} - I_{iK} - I_{iS} - I_{iK(ATP)} - \sum_j {}' g_c (V_i - V_j)$$

$$I_{iCa} = g_{Ca} M_\infty (V_i - V_{Ca}), \qquad \tau \frac{dN_i}{dt} = \lambda (N_\infty - N_i),$$

$$I_{iK} = g_K N_i (V_i - V_K), \qquad \tau_S \frac{dS_i}{dt} = S_\infty - S_i,$$

$$I_{iS} = g_S S_i (V_i - V_K),$$

$$I_{iK(ATP)} = g_{K(ATP)} p_i (V_i - V_K) \qquad g_{K(ATP)}(t) = \frac{g_1 - g_2}{[G_{in}(t - t_d)/G_K]^b f_D(J_i) + 1} + g_2$$

$$\frac{dC_i}{dt} = -\epsilon (\alpha I_{iCa} - M_S - M_P - M_N + M_{leak})$$

$$\frac{dG_{in}}{dt} = r_1 + r_2 - r_m$$

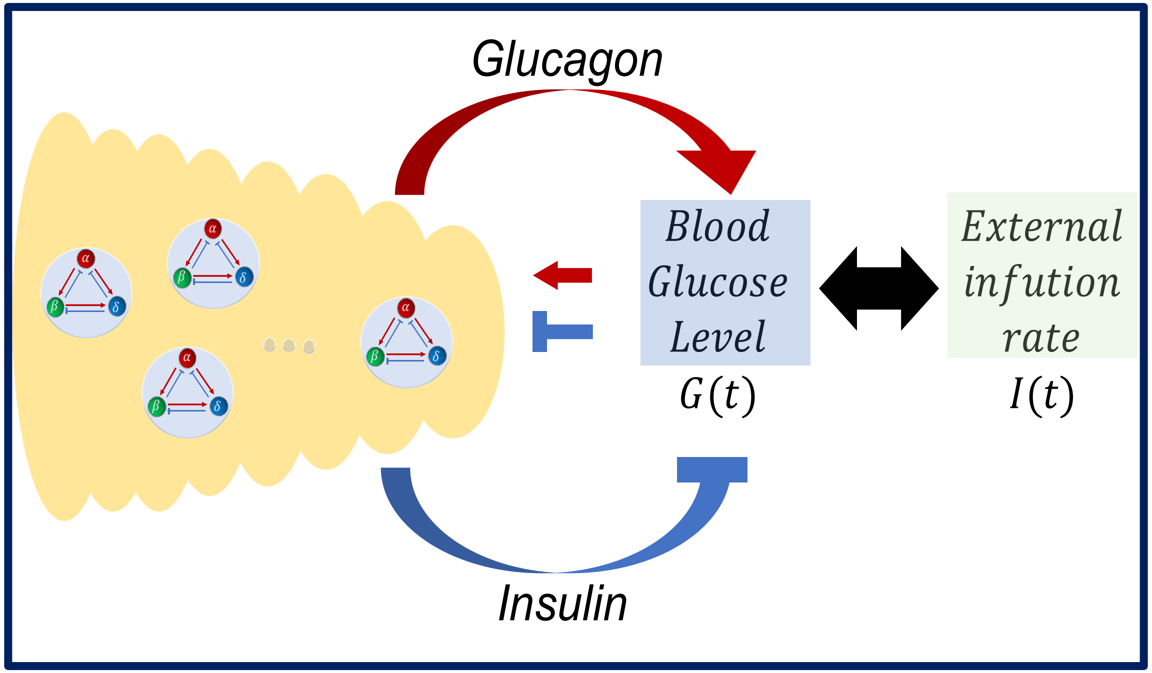
$g_{Ca}=3.6$	$V_{Ca}=25$ mV	$V_M=-20$ mV	$\theta_M=12$ mV	$\tau=20$ ms
$g_K=10$	$V_K=-75$ mV	$V_N=-17$ mV	$\theta_N=5.6$ mV	$\lambda=0.8$
$^*g_S=4$	$^*\gamma_1=1$	$^*V_S=-22$ mV	$^*\theta_S=8.0$ mV	$^*\tau_S=60$ s
$\alpha=1.3\times10^{-6}$ M/V s	$^*\gamma_2=1$	$^*\tau_p=0.30$ s	$^*n_{K(ATP)}=10^3$	$\Omega=1.5\times10^{-15}$ m^3
$\epsilon=0.01$	$\epsilon_{er}=0.01$	$^*\xi_{er}=1.0\times10^{-4}$	$\nu_{cyt}=10$ μm^3	$\nu_{er}=0.4$ μm^3
$g_1=3.0$	$g_2=0.6$	$G_K=2.8$ mM	$b=2.5$	$^*S_{max}=3.6\times10^{-17}$ mol
$^*M_S^{max}=246$ μM/s	$^*M_P^{max}=126$ μM/s	$^*k_N=84$ s^{-1}	$K_S=0.27$ μM	$K_P=0.50$ μM
$c_m=4.1\times10^{-5}$ M/s	$K_m=7.8$ mM	$^*R_0=1.2\times10^{-19}$ mol/s	$^*a_r=2.0\times10^{-3}$ s^{-1}	$[H^+]=10^{-7.40}$ M
$c_1=5.8\times10^{-4}$ M/s	$K_1=1.4$ mM	$c_2=5.3\times10^{-4}$ M/s	$K_2=17$ mM	$[K_a]=10^{-7.86}$ M
$^{**}k_0=1.8\times10^{-2}$ s^{-1}	$^{**}H_r=1.4\times10^{-2}$ mM	$^{**}H_J=1.4\times10^{-4}$ mM	$^{**}t_d=90$ s	$^{**}m=4.0$
$^{**}H_0=0$ mM	$^*C_0=10^{-4}$ mM	$^*C_b=6.0\times10^{-5}$ mM		

Take home message #2

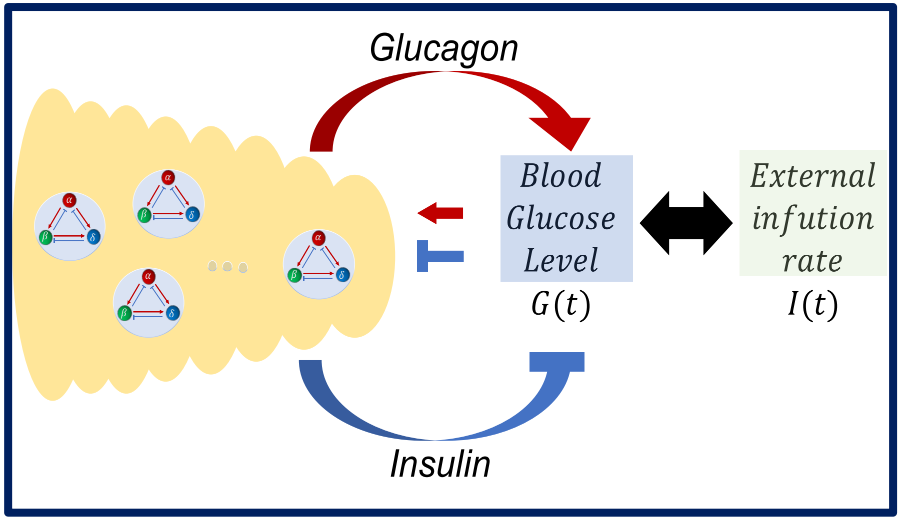
"Things should be as simple as possible, but not simpler"…물리학자의 처지에서 좀 더 자세히 설명해보면 …(중략)… 즉, 중요하지 않은 것은 버리고 버려 정말 단순한 기본 모형에서 출발해야 한다. 하지만 정도를 벗어나, 마치 목욕물과 함께 아기를 버리는 것처럼 가장 중요한 것 까지 버리는 그런 정도의 극단적 단순화를 해서는 안된다.

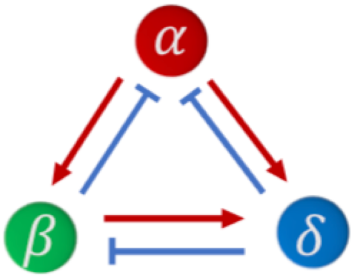
김범준저 '세상 물정의 물리학'

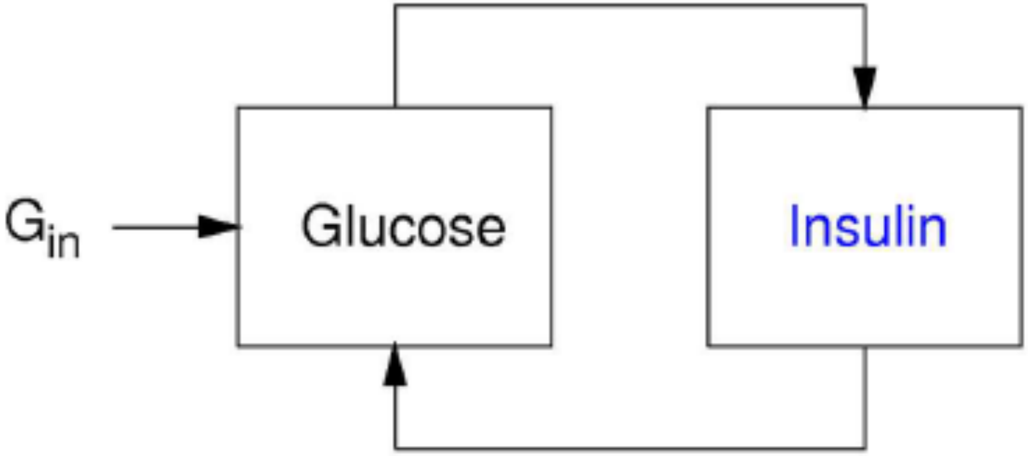
Modeling for glucose homeostasis



Taegeun Song and Junghyo Jo, Phys. Biol (2019)

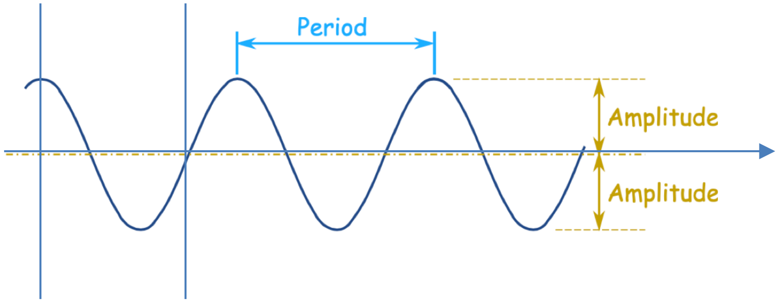

Glucagon
Blood Glucose Level
G(t)
External infution rate
I(t)
Insulin

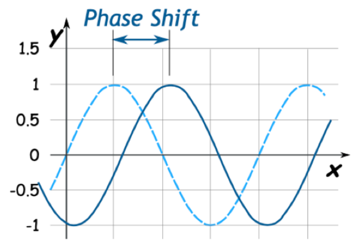

α
β
δ

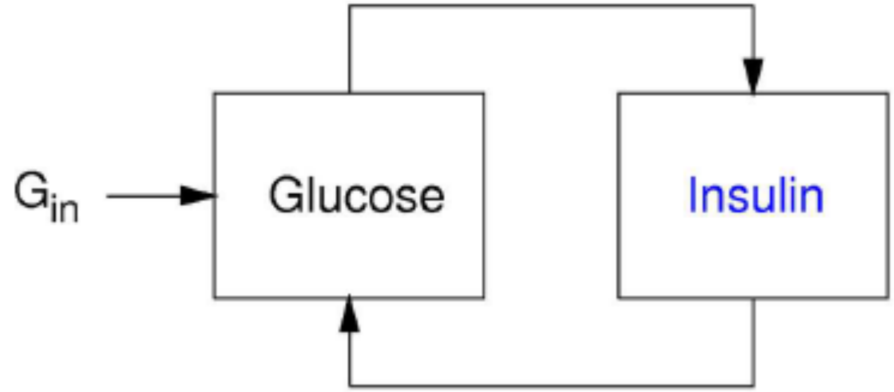

G_in
Glucose
Insulin

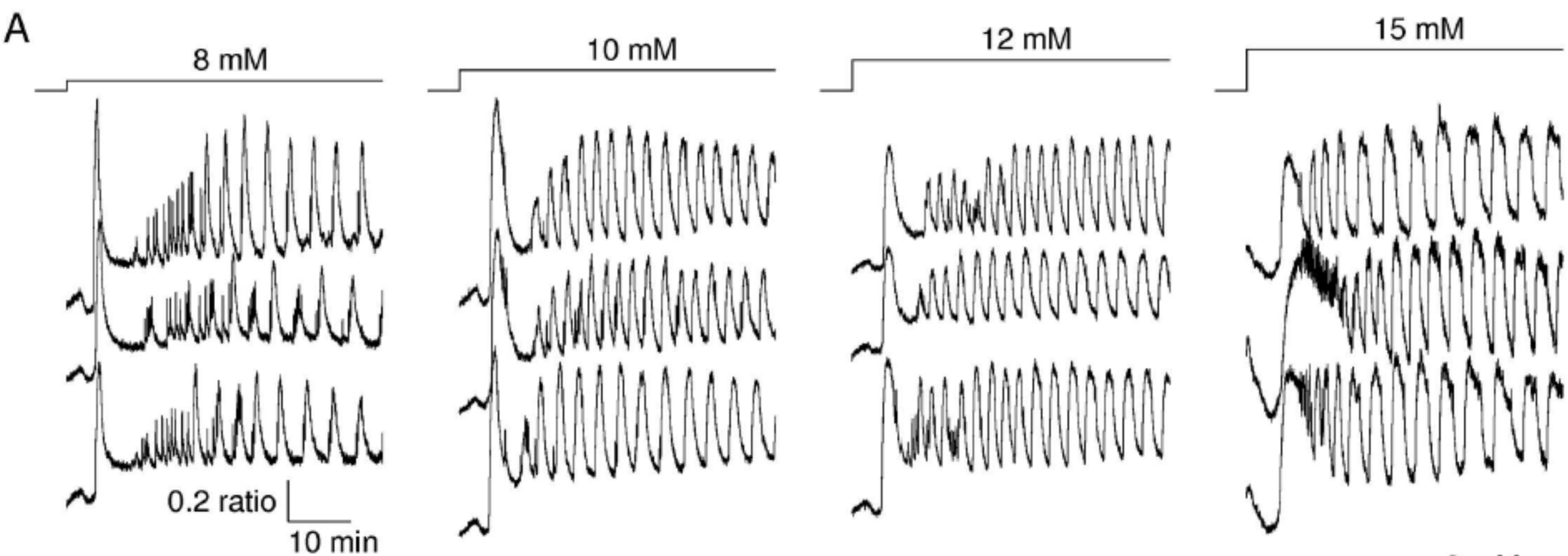

β

Amplitude & phase



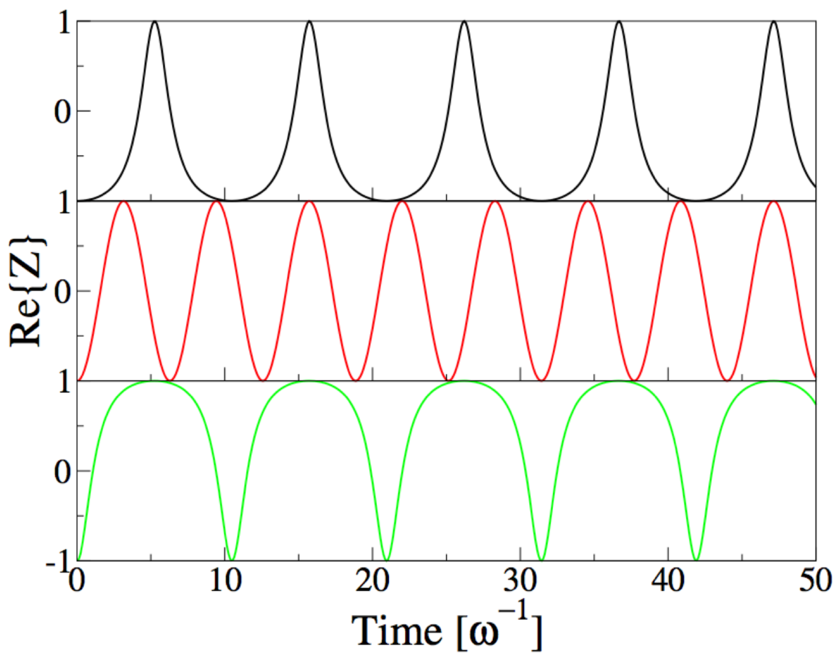






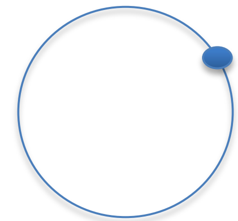
Active rotator

$$\dot{\theta} = \omega_0 - \mu \cos\theta$$



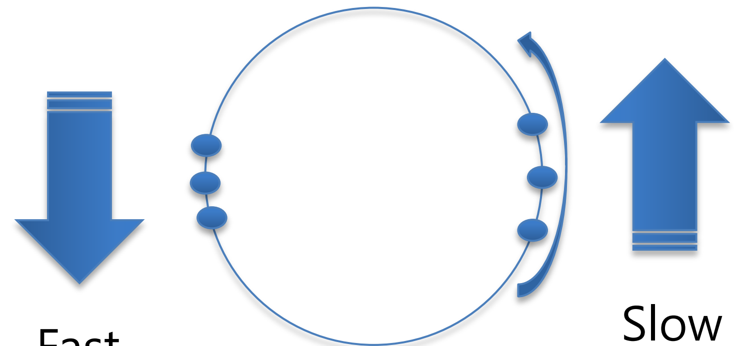
Active/silent phase described by phase modulation

$\frac{\mu}{\omega_0} >= 1$



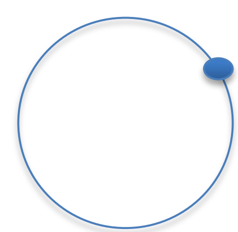
Phase locked at

$$\cos^{-1}\left|\frac{\omega_0}{\mu}\right|$$



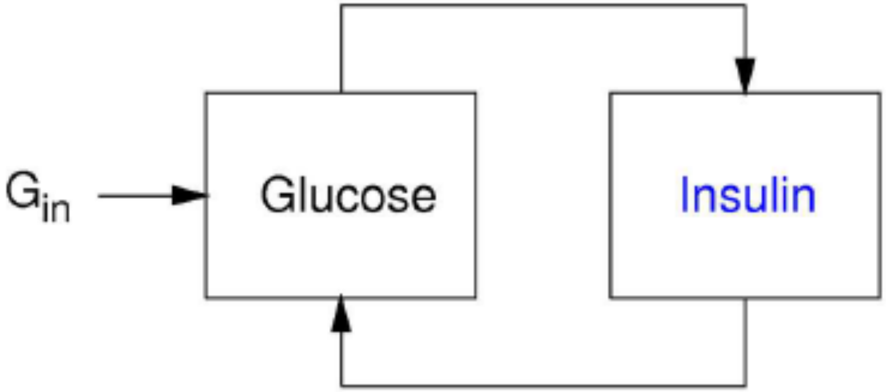
Self-sustained oscillation

$\frac{\mu}{\omega_0} =< -1$

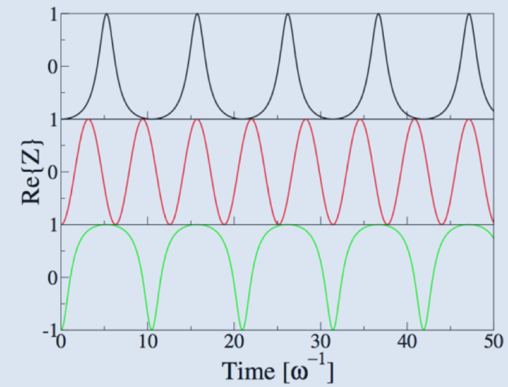


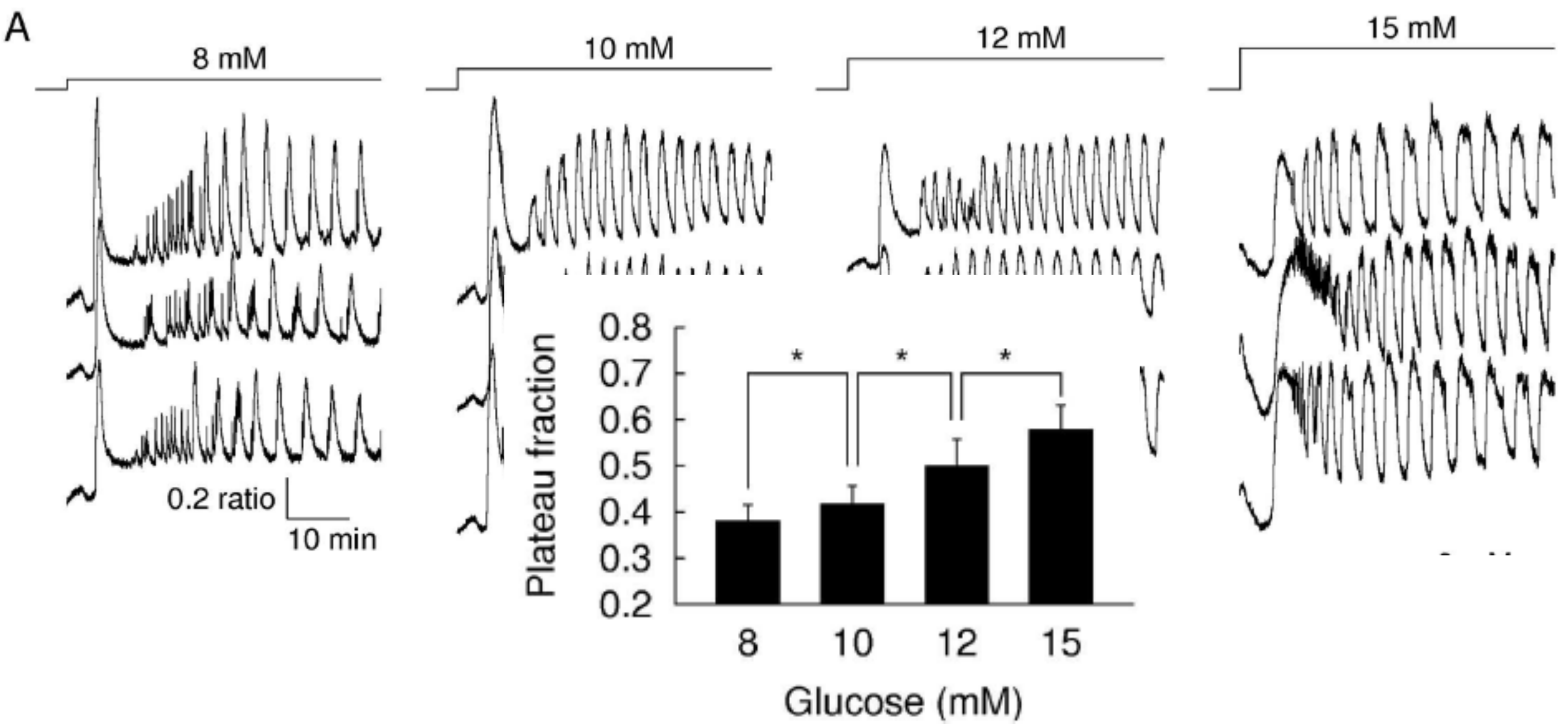
Phase locked at

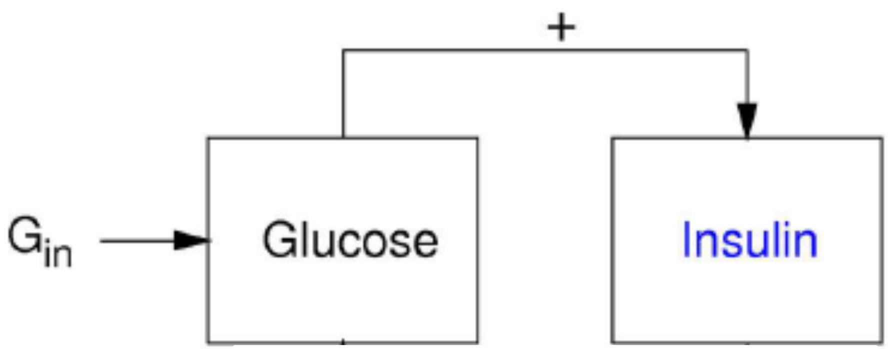
$$\cos^{-1}\frac{\omega}{\mu}$$



$$\dot{\theta} = \omega_0 - \mu \cos \theta$$







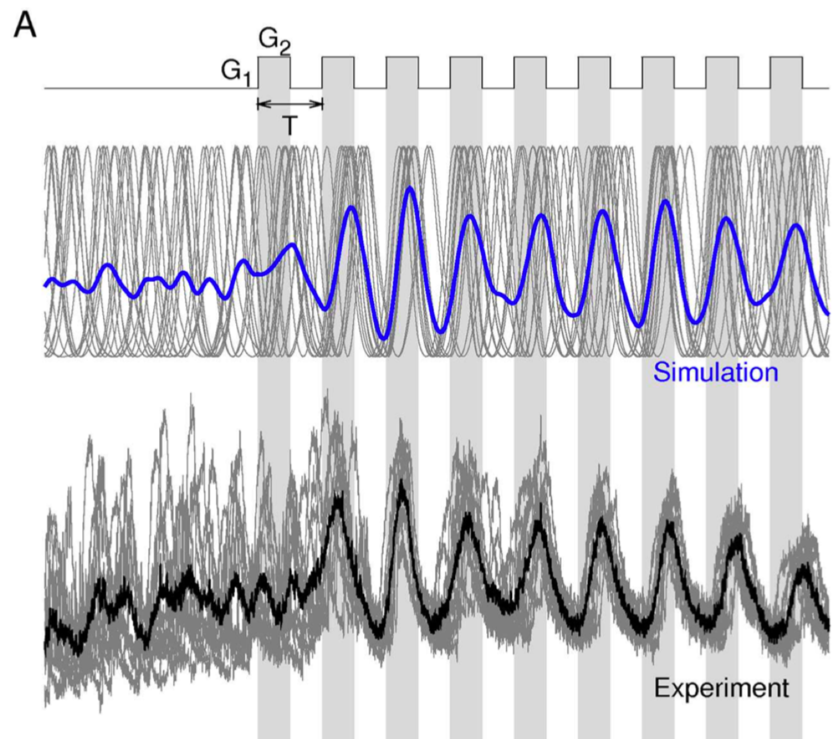
$$\frac{d\theta_n}{dt} = \omega_n - \mu(G)\cos\theta_n$$

$$\mu(G) = \bar{\mu}\sinh\left(\frac{G - G_0^{\mu}}{\delta G^{\mu}}\right)$$

$$I = N^{-1}\sum_{n=1}^{N} r(G)(1 + \cos\theta_n)$$

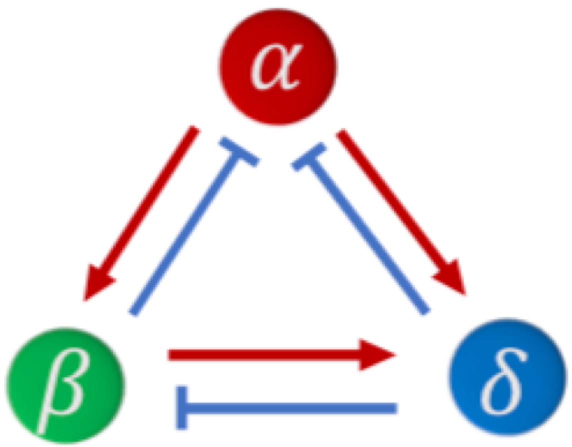
$$r(G) = 0.25[1 + \tanh[(G - G_0^{r})/\delta G^{r}]]$$

$$\frac{dG}{dt} = G_{in} - v\, I \cdot G$$



PLoS ONE 12 (2): e0172901(2017)

Biophysical model for islets

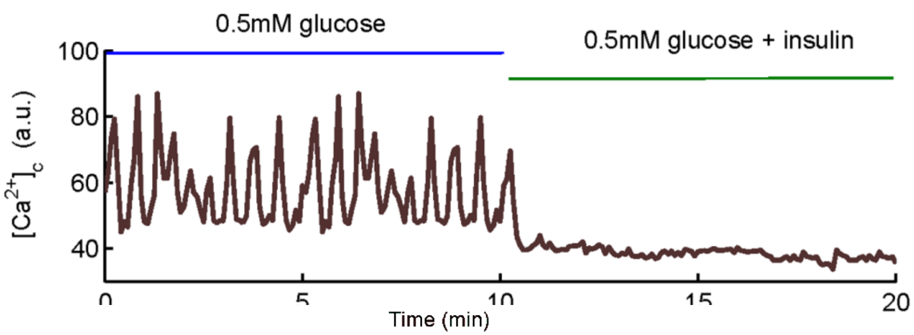


Interaction	Sign	Mediater	Reference
$\alpha \to \alpha$	$A_{\alpha\alpha} = 1$	Glucagon, Glutamate	[121–124]
$\alpha \to \beta$	$A_{\beta\alpha} = 1$	Glucagon, Glutamate, Acetylcholine	[59, 60, 62, 125]
$\alpha \to \delta$	$A_{\delta\alpha} = 1$	Glucagon, Urocortin3	[63–66, 76]
$\beta \dashv \alpha$	$A_{\alpha\beta} = -1$	Insulin, GABA, Zn^{2+}, ATP, Serotonin	[8, 24, 67–73, 126]
$\beta \to \beta$	$A_{\beta\beta} = 1$	Insulin, GABA, ATP	[127–132]
$\beta \to \delta$	$A_{\delta\beta} = 1$	Insulin, Urocortin3	[74–76]
$\delta \dashv \alpha$	$A_{\alpha\delta} = -1$	Somatostatin	[4, 5, 8, 9, 55]
$\delta \dashv \beta$	$A_{\beta\delta} = -1$	Somatostatin	[4, 5, 8, 9, 52, 133]
$\delta \to \delta$	$A_{\delta\delta} = 1?$	-	unknown

$$\dot{r}_{n\sigma} = \tau_r^{-1}\left[f_\sigma(G) - r_{n\sigma}^2\right] r_{n\sigma} + K \sum_{\sigma'} A_{\sigma\sigma'} r_{n\sigma'} \cos(\theta_{n\sigma'} - \theta_{n\sigma}),$$

$$\dot{\theta}_{n\sigma} = \omega_{n\sigma} - g_{n\sigma}(G)\cos\theta_{n\sigma} + K \sum_{\sigma'} A_{\sigma\sigma'} \frac{r_{n\sigma'}}{r_{n\sigma}} \sin(\theta_{n\sigma'} - \theta_{n\sigma}),$$

Ex) Experiment for $A_{\alpha\beta}$

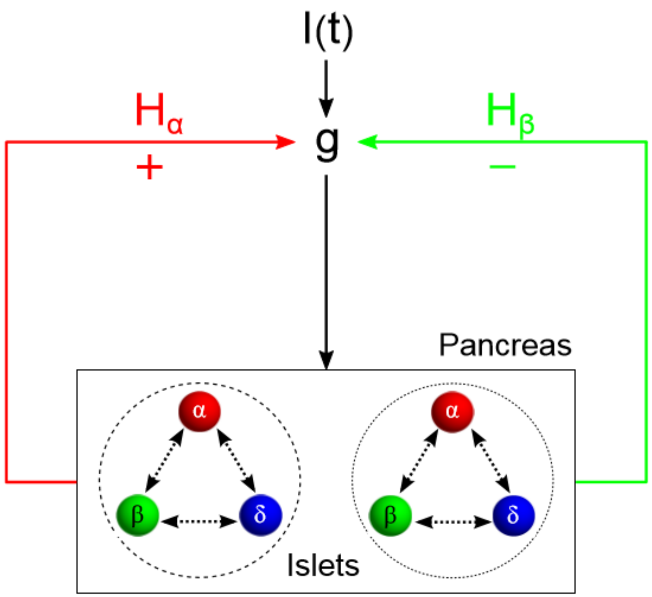


PLoS One.7, e32282 (2012)

Hormone define

$$H_{n\sigma} \equiv r_{n\sigma}(\cos\theta_{n\sigma} + 1)$$

Biophysical model of glucose homeostasis

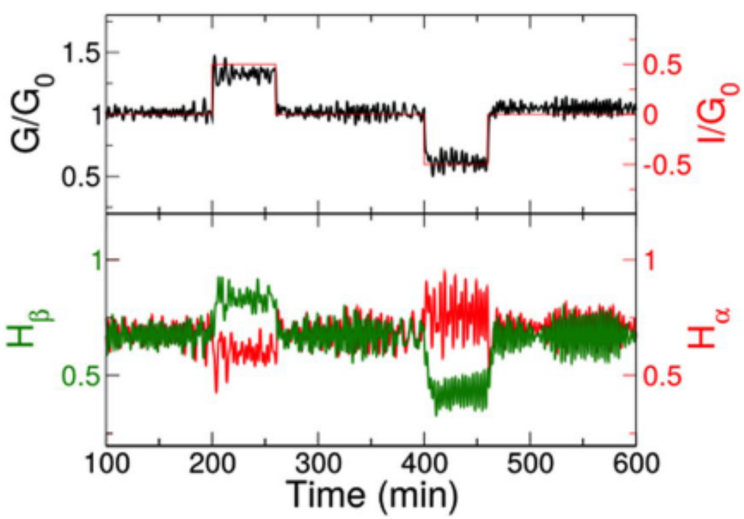


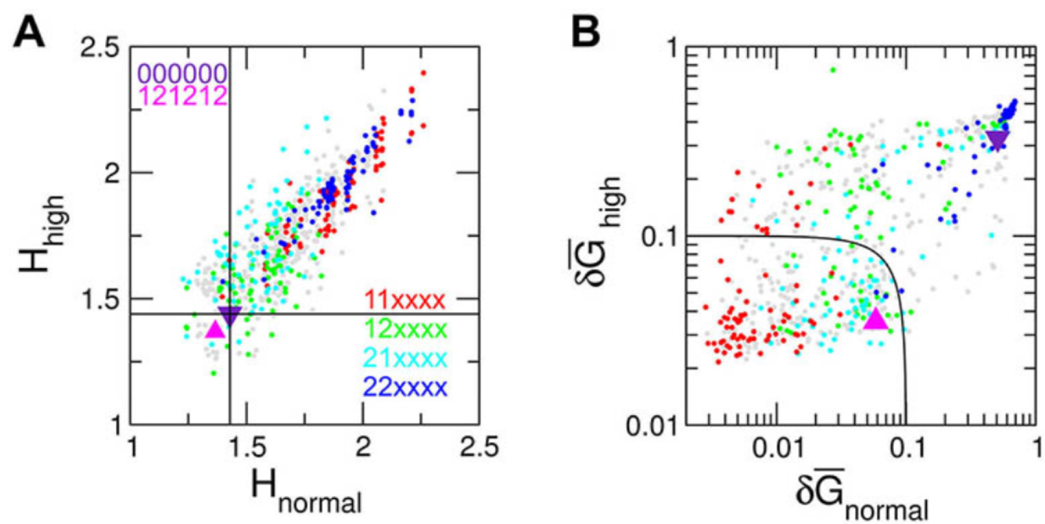
$$\dot{r}_{n\sigma} = \tau_r^{-1}\left[f_\sigma(G) - r_{n\sigma}^2\right] r_{n\sigma} + K\sum_{\sigma'} A_{\sigma\sigma'} r_{n\sigma'} \cos(\theta_{n\sigma'} - \theta_{n\sigma}),$$

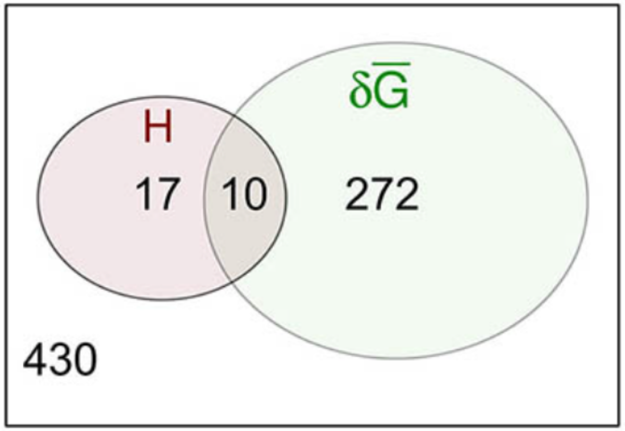
$$\dot{\theta}_{n\sigma} = \omega_{n\sigma} - g_{n\sigma}(G)\cos\theta_{n\sigma} + K\sum_{\sigma'} A_{\sigma\sigma'} \frac{r_{n\sigma'}}{r_{n\sigma}} \sin(\theta_{n\sigma'} - \theta_{n\sigma}),$$

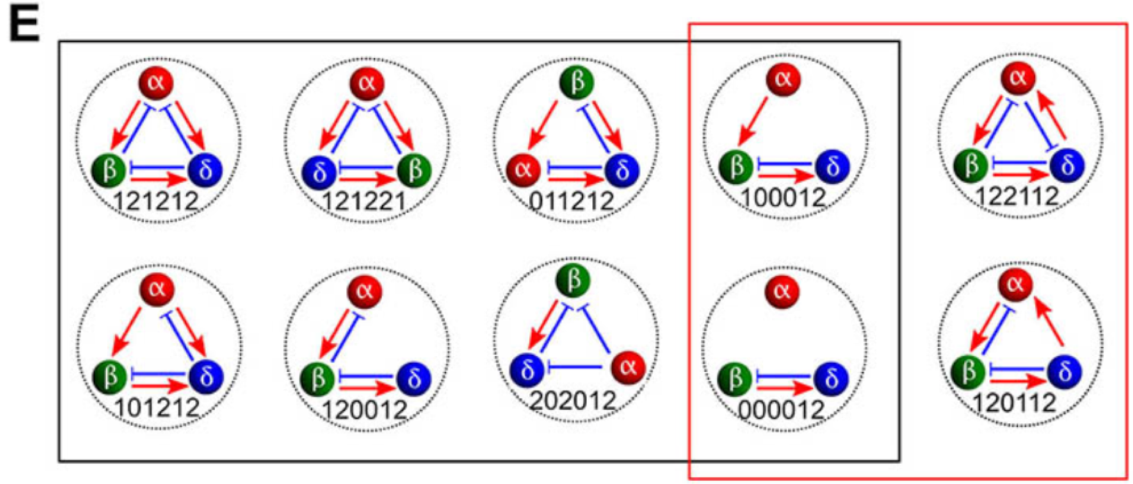
$$\dot{G} = \lambda\left[G_0 \underline{\sum_{n=1}^{N} r_{n\alpha}(1+\cos\theta_{n\alpha})} - G \underline{\sum_{n=1}^{N} r_{n\beta}(1+\cos\theta_{n\beta})}\right] + I(t).$$

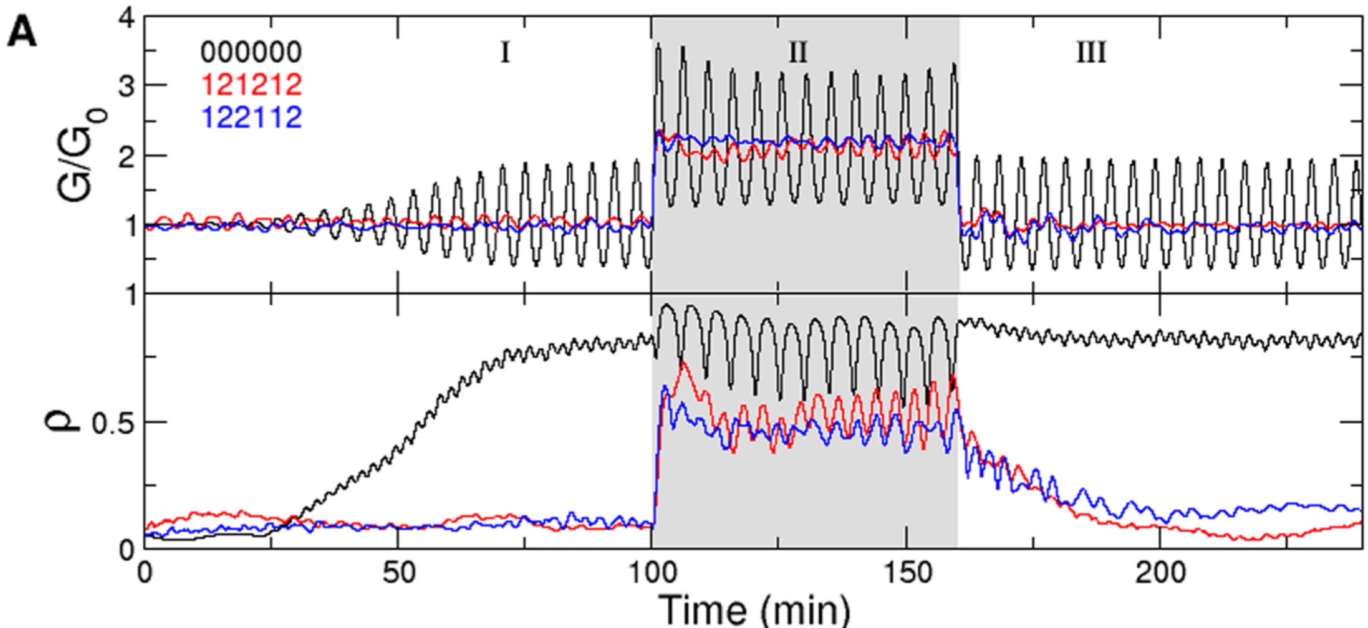
Total glucagon   Total Insulin



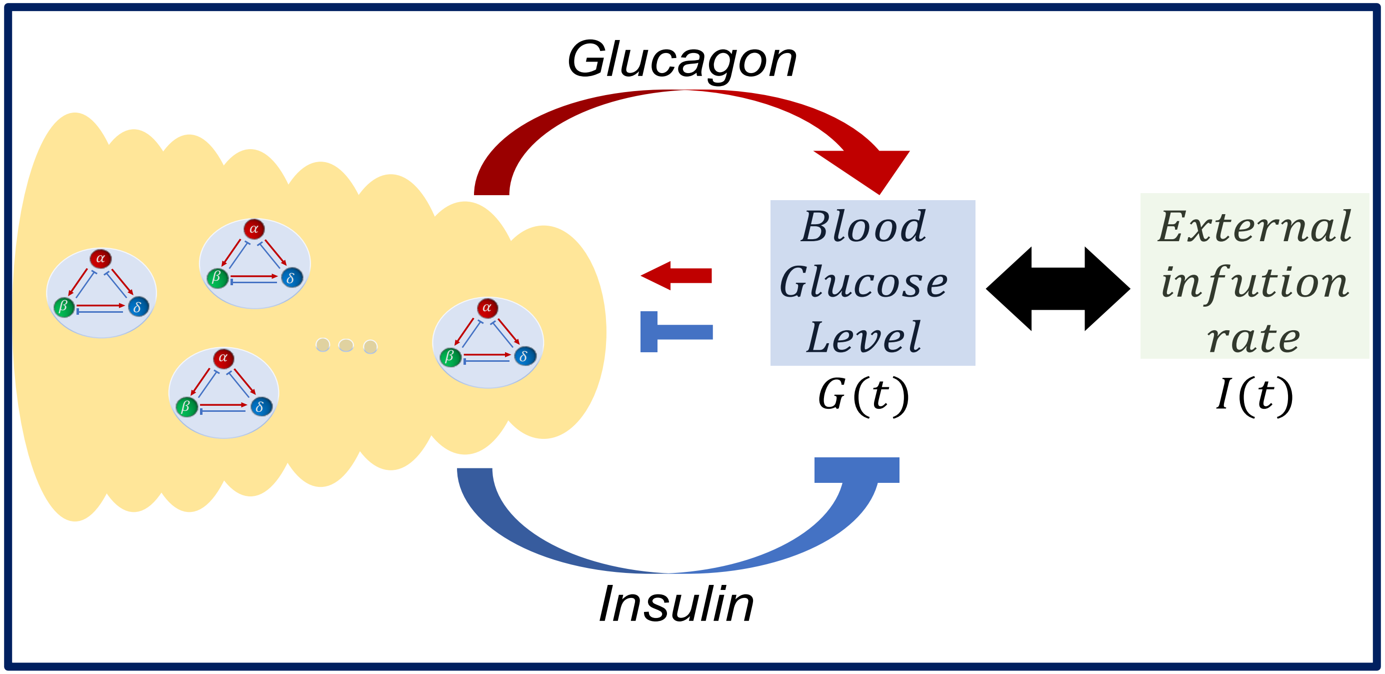








Controllable synchronization !

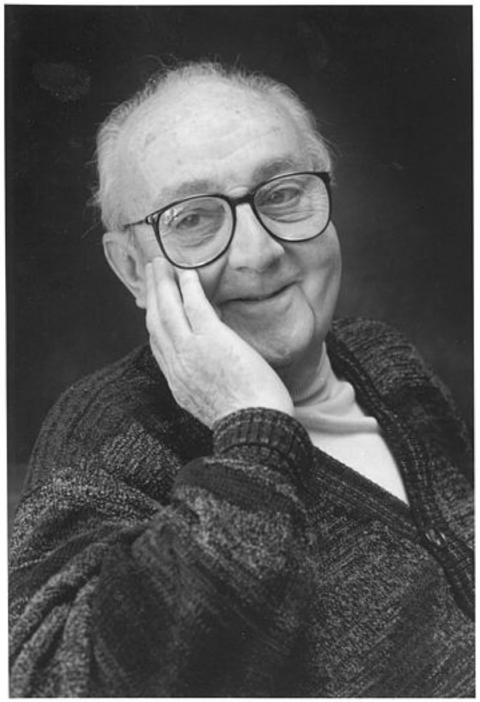


Specific coupling structure, efficient and tight blood glucose level control via controlling synchronization !

Take home message #3

진화의 산물로 존재하는 생체 시스템은 효과적이고 효율적인 상태에 놓여 있다 !?

George Box



Born	18 October 1919 Gravesend, Kent, England
Died	28 March 2013 (aged 93) Madison, Wisconsin

Famous aphorism

Essentially,
all models are wrong,
but some are useful.

Empirical Model-Building and Response Surfaces, p. 424, Wiley. ISBN 0471810339.

Let me make it useful !

Failure of glucose homeostasis : diabetes mellitus

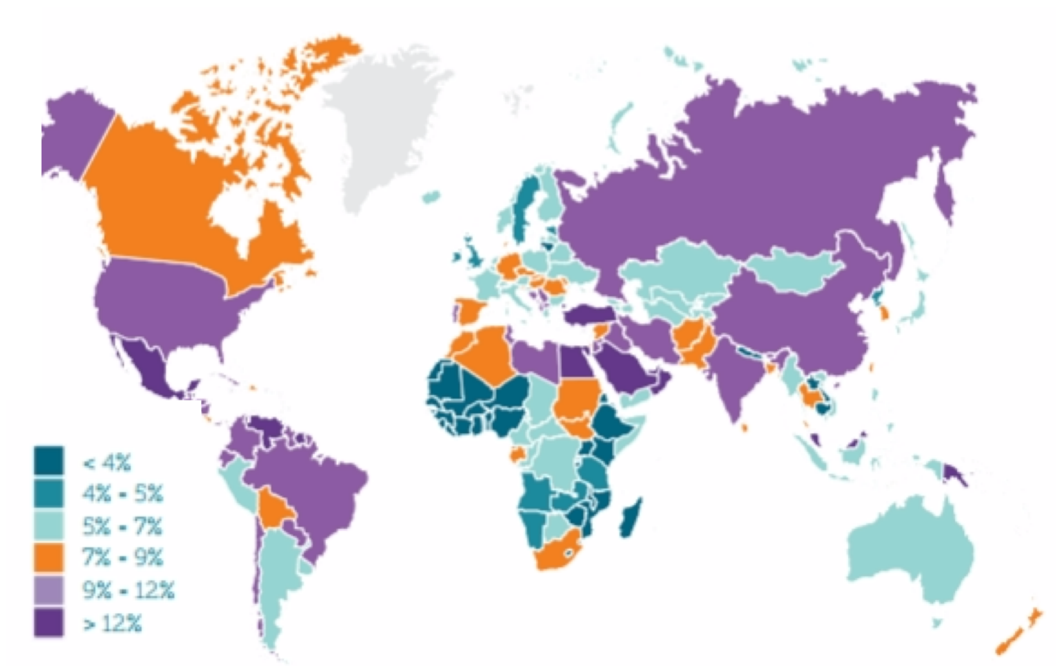
International Diabetes Federation

world diabetes day 14 November

Type 1 DM : failure to produce enough insulin (~10%)

Type 2 DM : insulin resistance, a condition in which cells fail to respond to insulin properly (~90%)

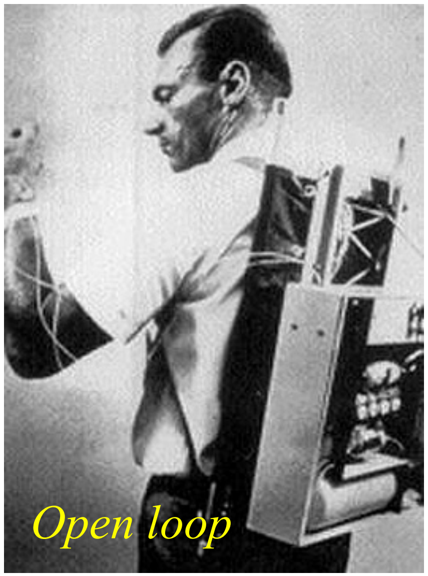
Gestational diabetes : woman without diabetes develops high blood sugar levels during pregnancy



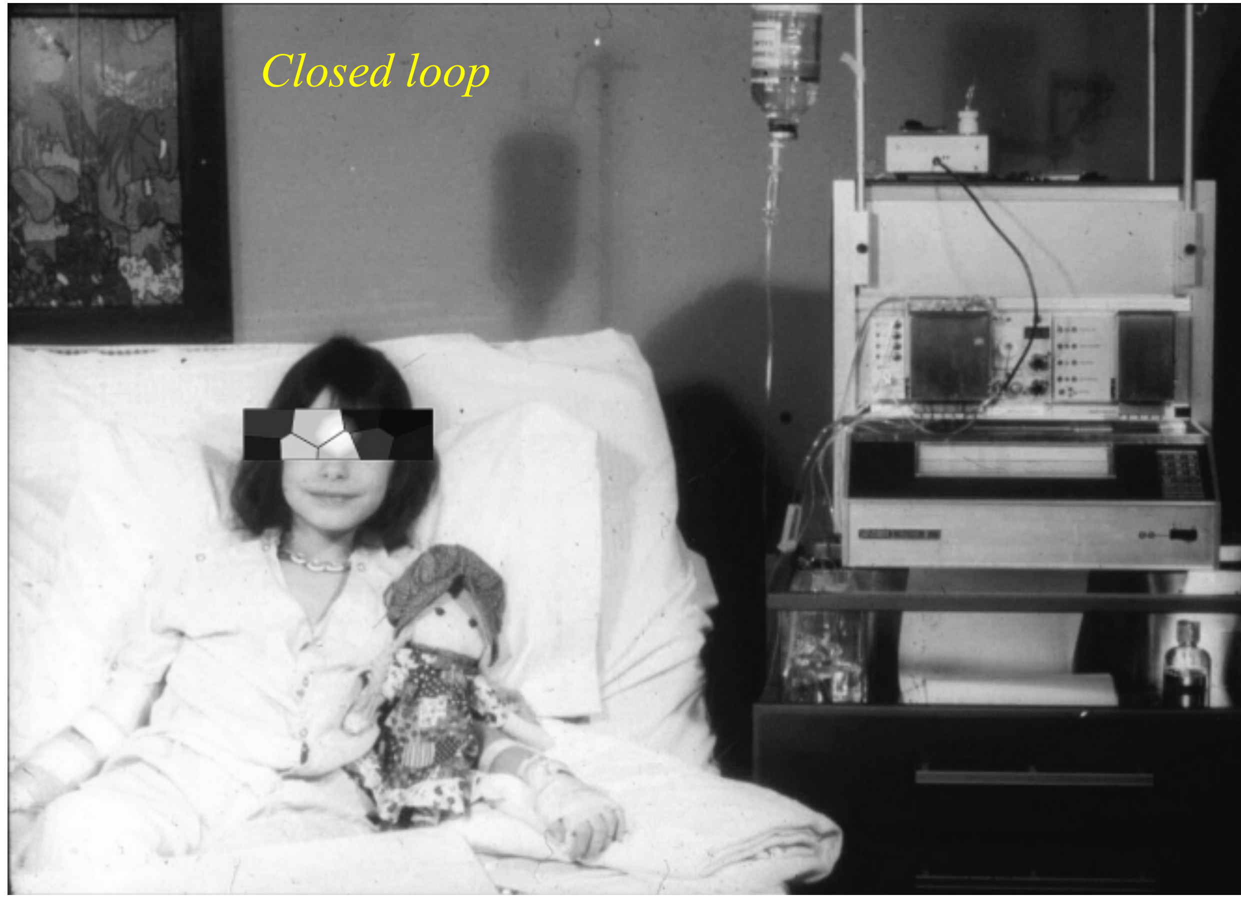
OhealthNews, Kyoung Hee University Healthcare system

Diabetes mellitus is a chronic disease, for which there is no known cure in general

Artificial pancreas



1963, insulin pump

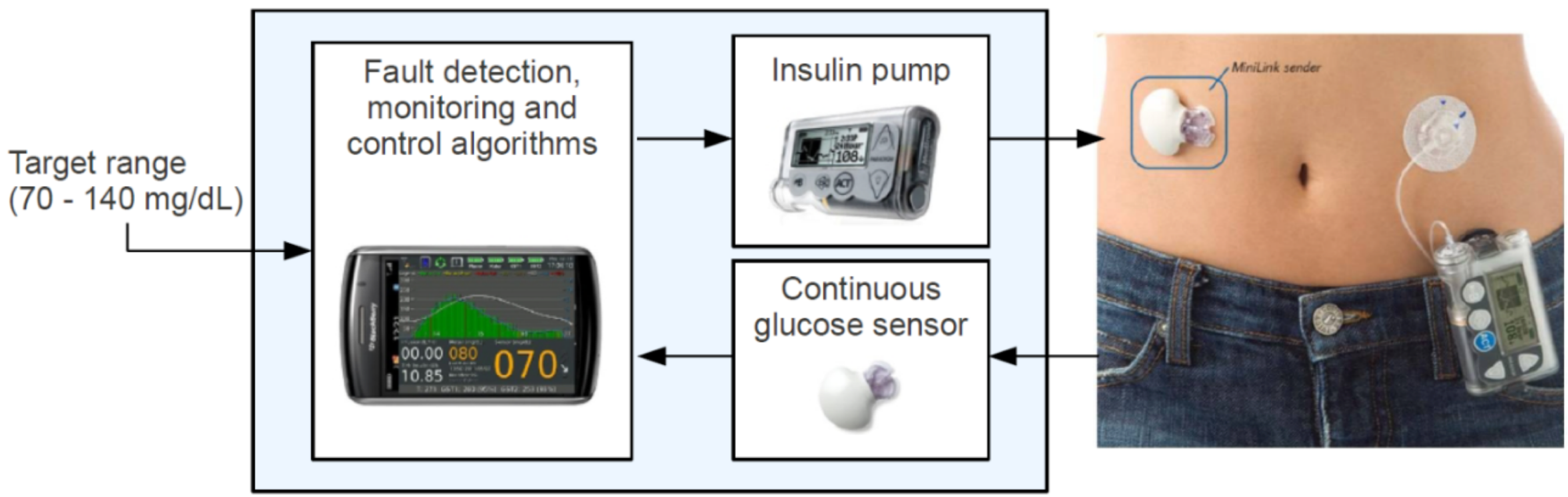


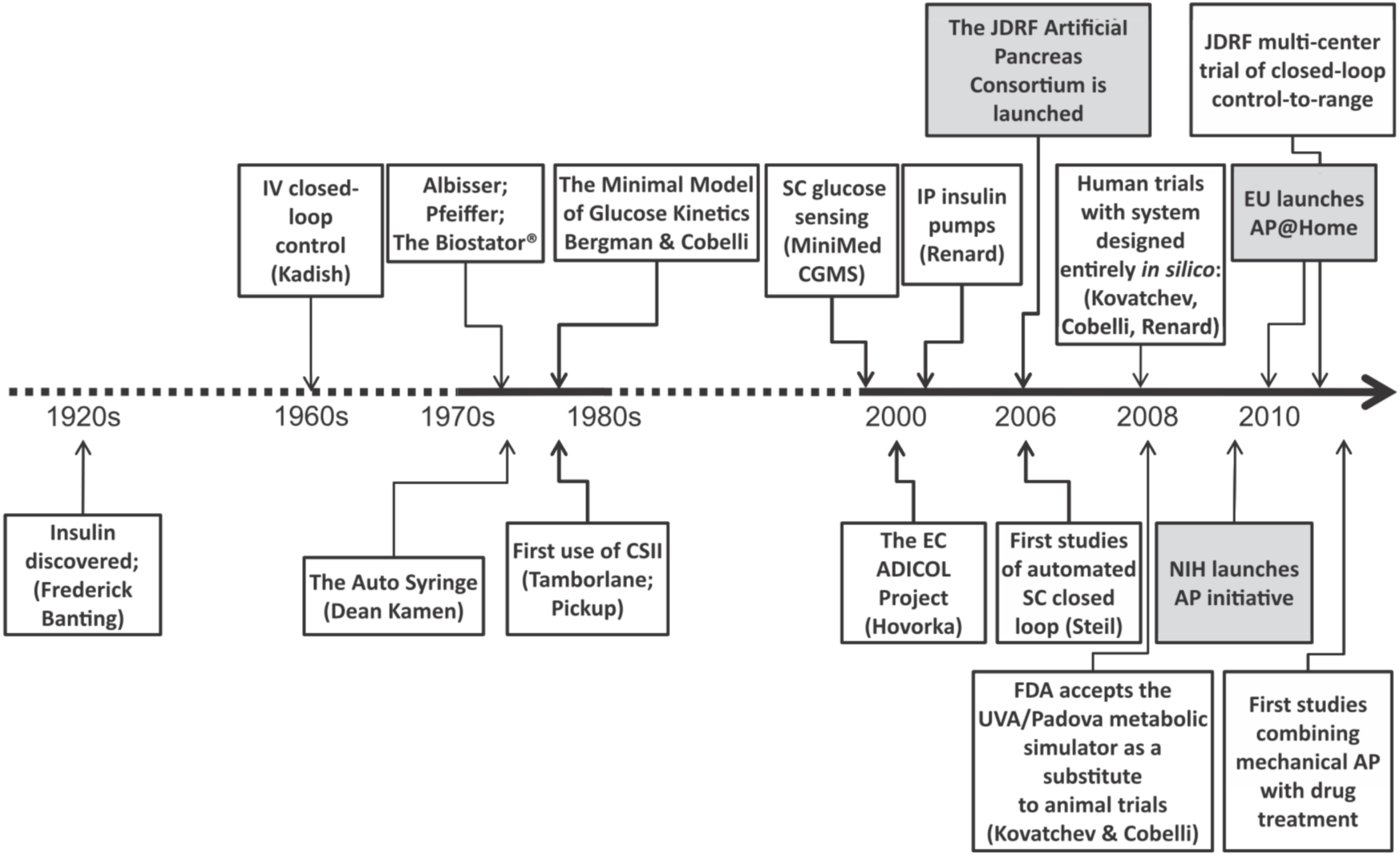
1977, Biostator

Cf. The GOD ver.

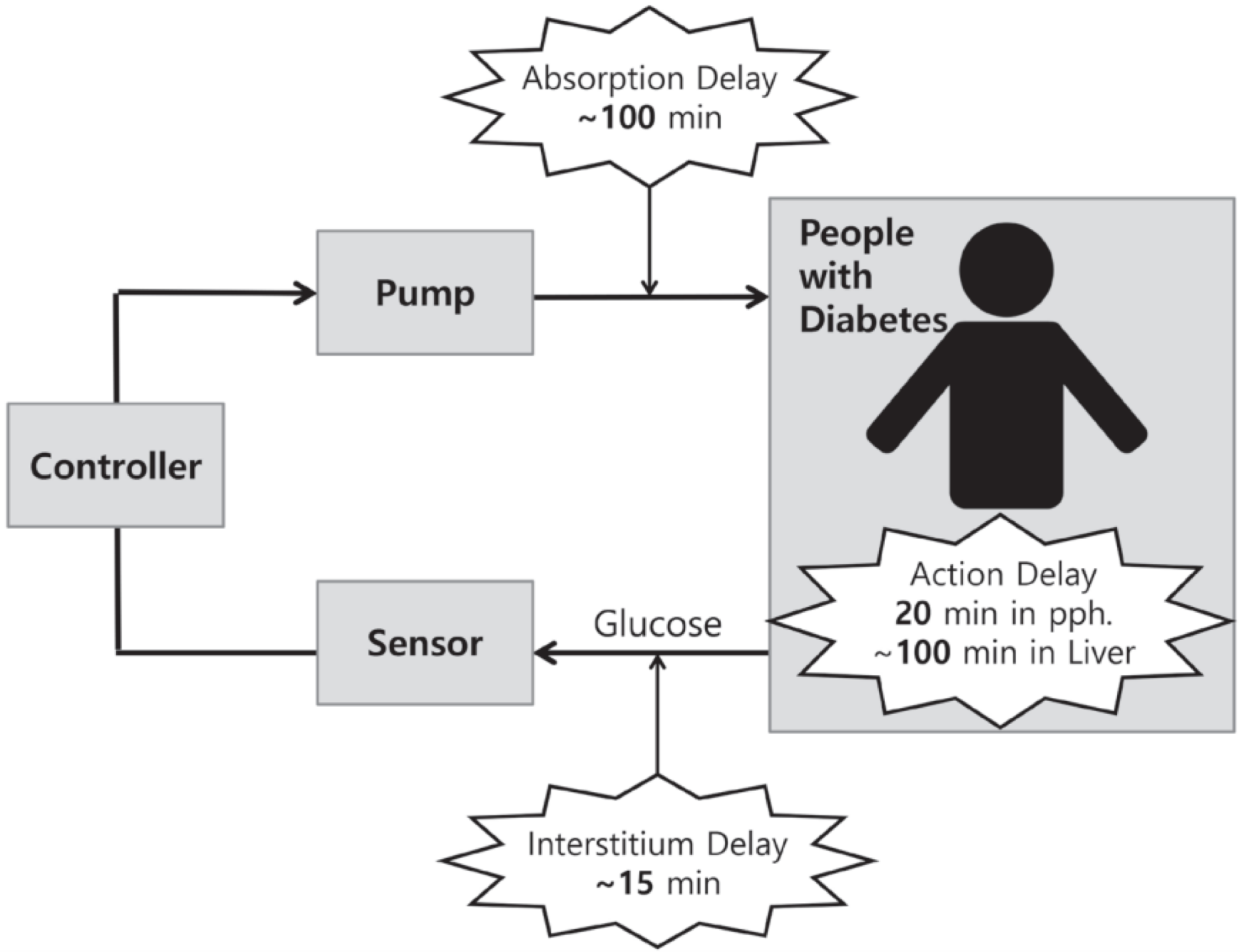
300 million X 1000 cells X Volume $\frac{4}{3}\pi(100\mu m)^3$ X density 1 g/cm^3 ~ 1 g

Portable Artificial Pancreas

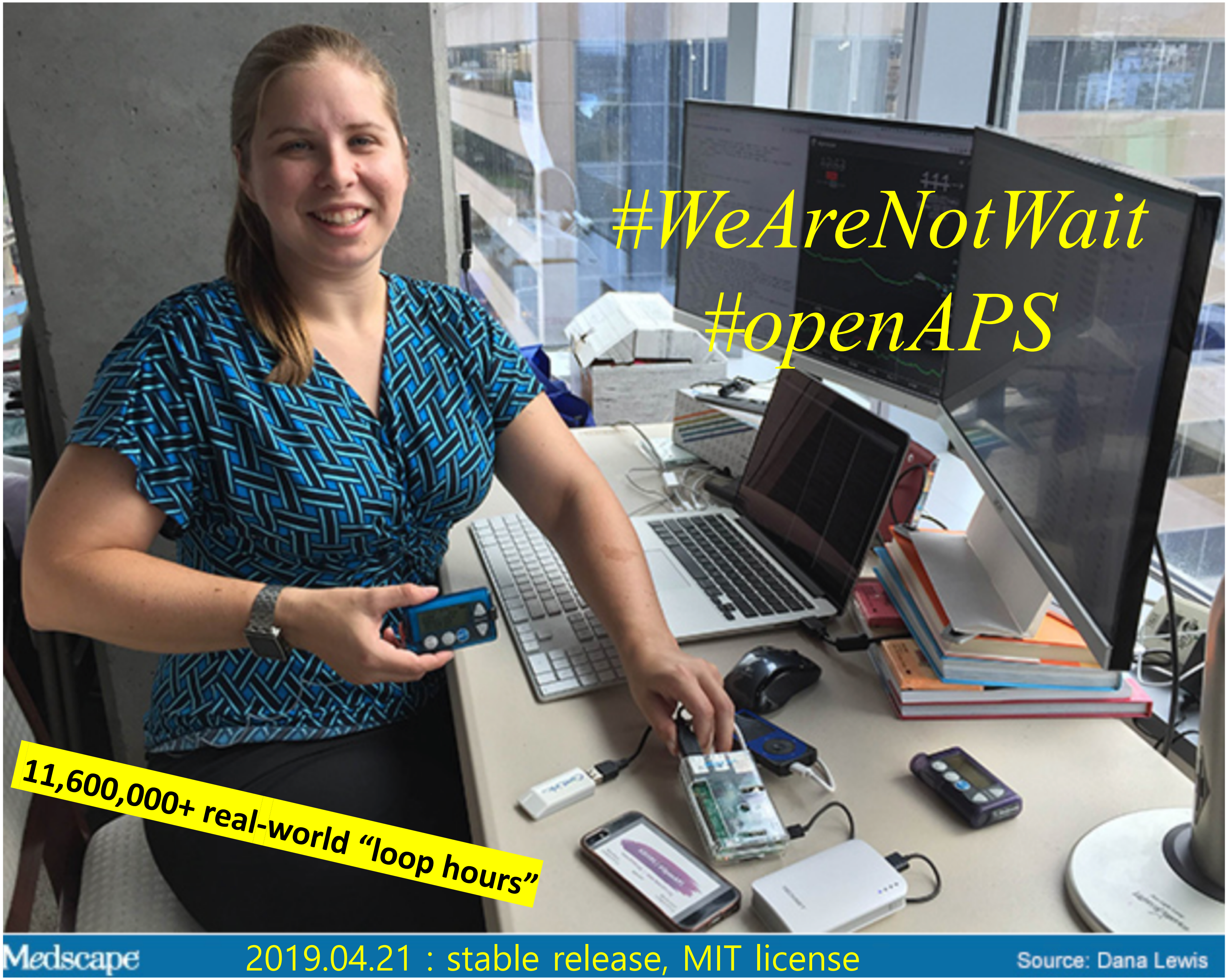


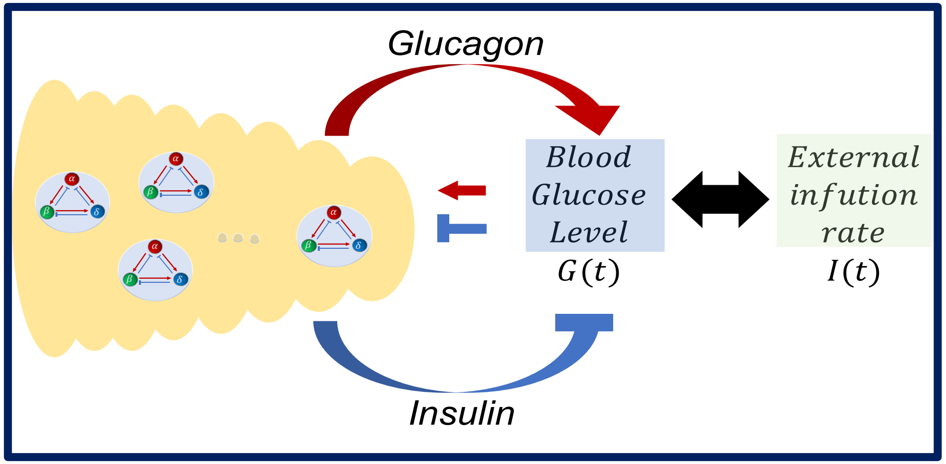


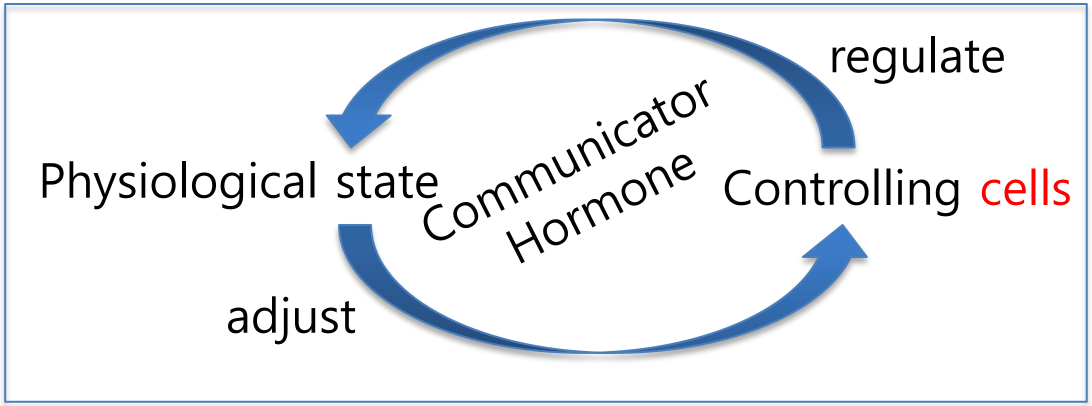
2016.09.28 : FDA approved the Medtronic Minimed 670G

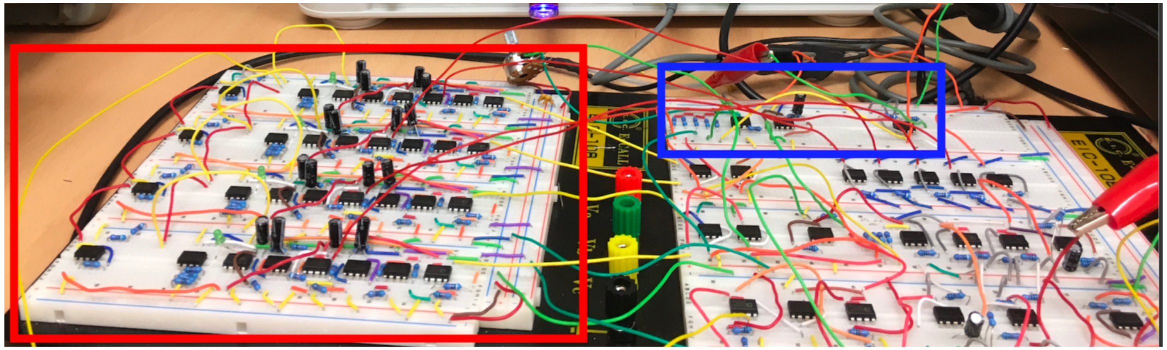


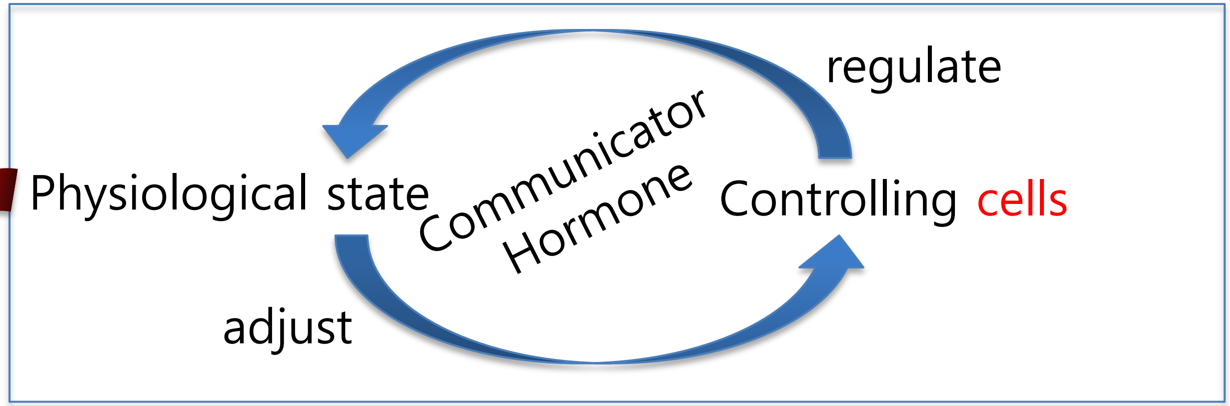
J Korean Diabetes 2017;18:141-149
https://doi.org/10.4093/jkd.2017.18.3.141

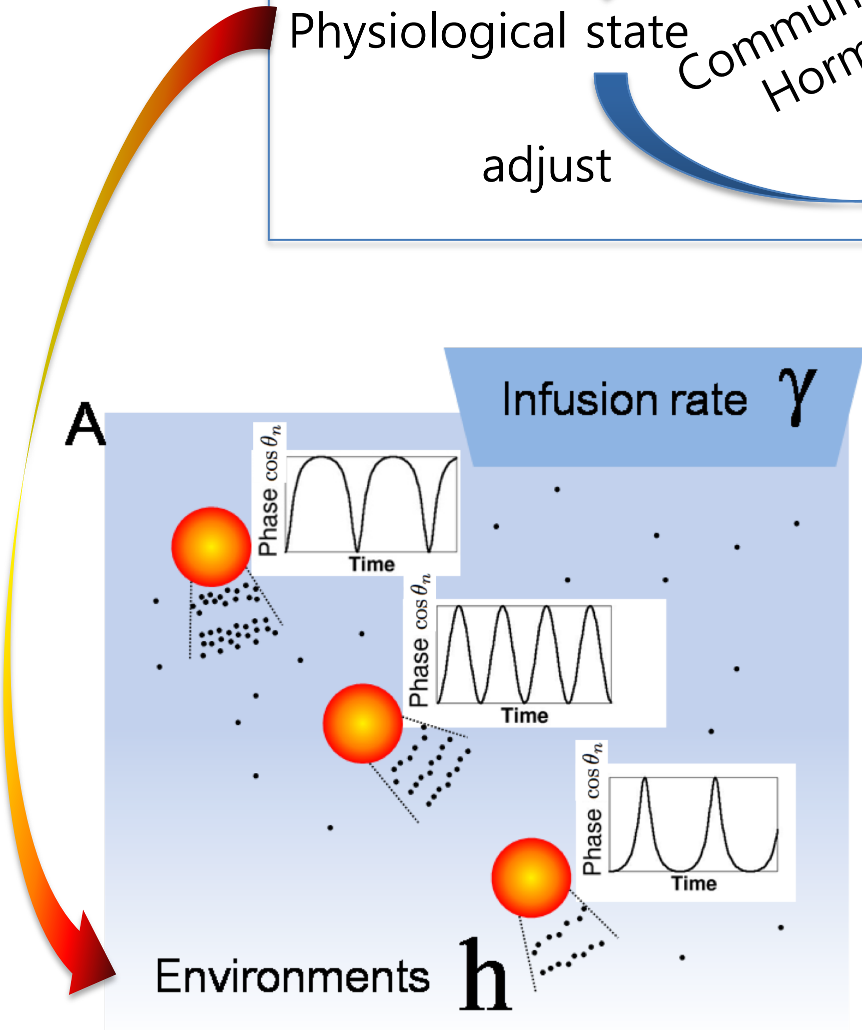

#WeAreNotWait
#openAPS
11,600,000+ real-world "loop hours"
Medscape
2019.04.21 : stable release, MIT license
Source: Dana Lewis


Glucagon
Blood Glucose Level
$G(t)$
External infution rate
$I(t)$
Insulin


regulate
Physiological state
Communicator
Hormone
Controlling cells
adjust







$$\dot{\theta}_n = \omega_0 - \mu(h)\cos\theta_n$$

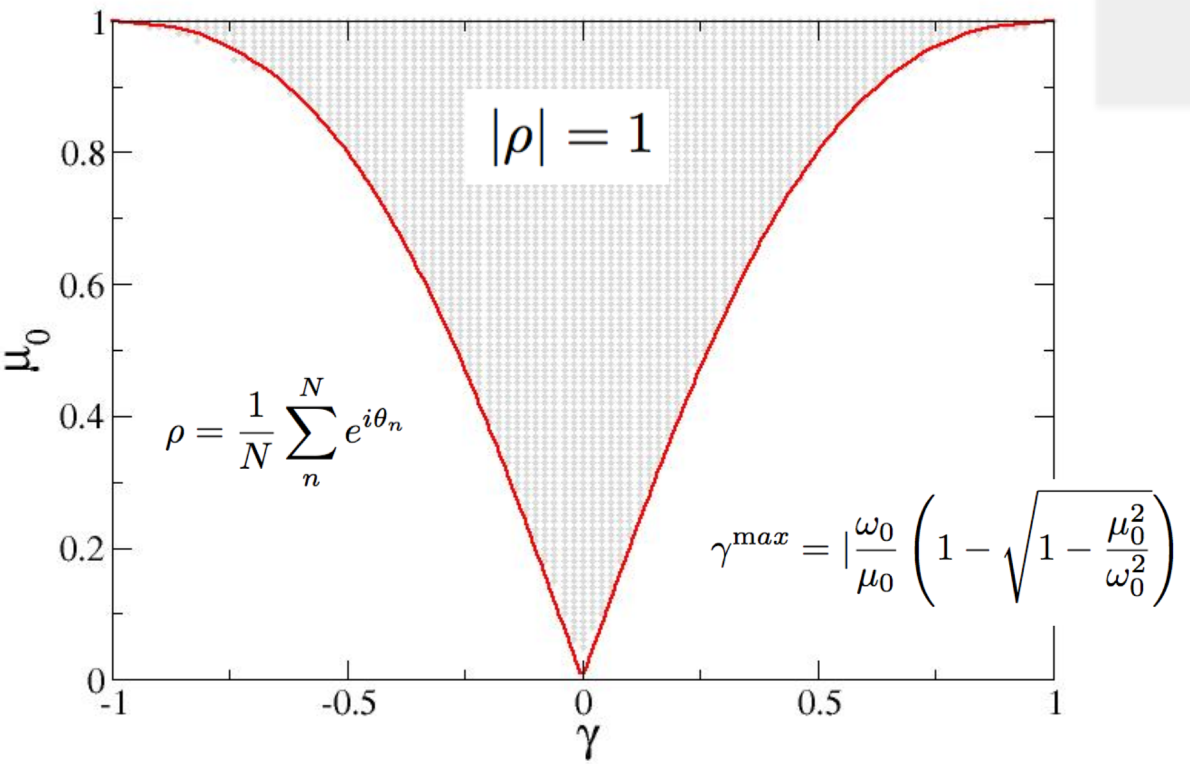
$$\dot{h} = \gamma - \frac{1}{N}\sum_{n=1}^{N}\cos\theta_n$$

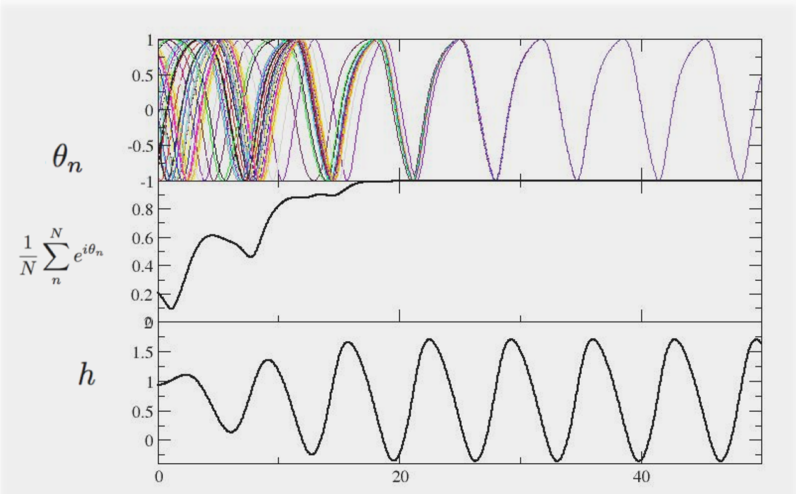
Mean field, negative feedback btw multiple effectors and environment

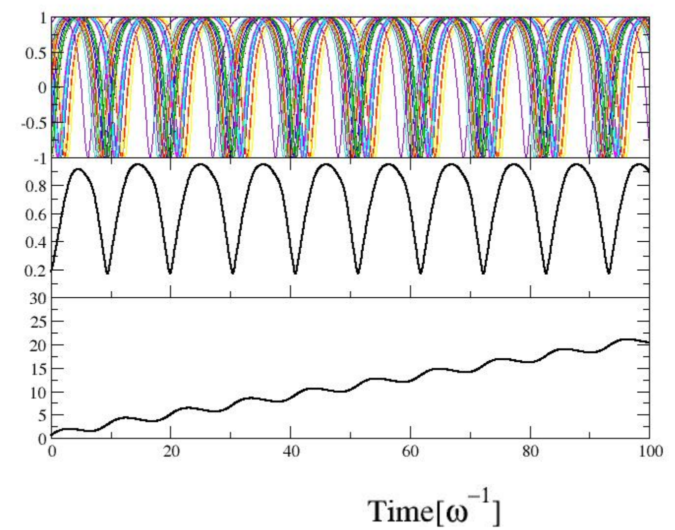
$$\dot{\theta}_n = \omega_0 - \mu(h)\cos\theta_n$$

$$\dot{h} = \gamma - \frac{1}{N}\sum_{n=1}^{N}\cos\theta_n$$

$\mu(h)$: any monotonic function varying btw $\pm\mu_0$







Prefer choice of γ, we can find *entrainment* without periodic signal

Demonstration of the controlling synchronization

Realization !

$$\dot{\theta}_n = \omega_0 - \mu(h)\cos\theta_n$$

$$\dot{h} = \gamma - \frac{1}{N}\sum_{n=1}^{N}\cos\theta_n$$

$$\frac{1}{N}\sum_n Cos\theta_n \stackrel{\text{def}}{=} X$$

$$\frac{1}{N}\sum_n Sin\theta_n \stackrel{\text{def}}{=} Y$$

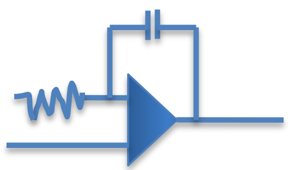
$$\dot{X} = (\mu(h)X - \omega_0)Y$$

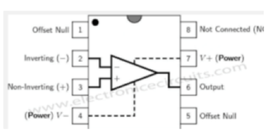
$$\dot{Y} = \omega_0 X - \frac{\mu(h)}{2}(X^2 - Y^2 + 1)$$

$$\dot{h} = \gamma - X$$

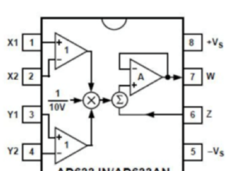
Operational Amplifier

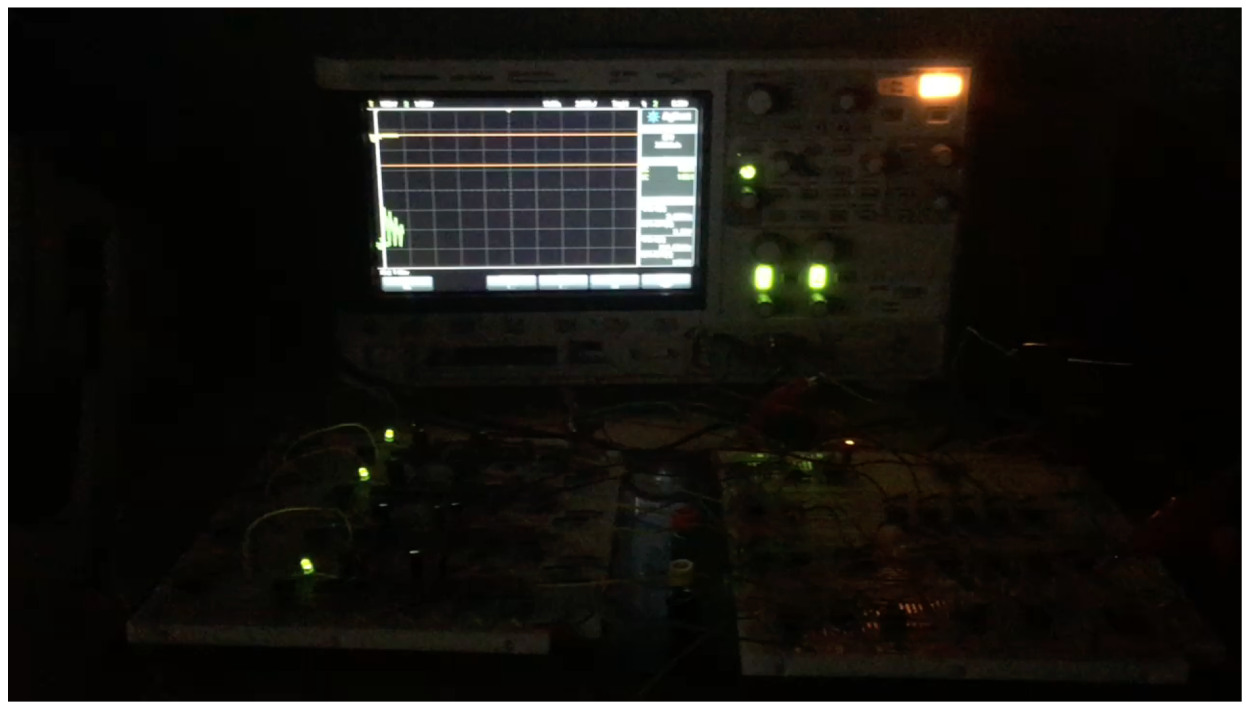
Integrator





Multiplier : AD633





Thank you very much for your attention !

Welcome to any question !

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