Phase Modulation of Hormonal Oscillations

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[One sentence summary] Intra-islet network modulates inter-islet synchronization for glucose homeostasis.

Dynamic equilibrium is maintained by counter-regulating elements in living systems. The pancreatic α and β cells produce glucagon and insulin for glucose homeostasis. They exist in multiple micro-organs, the islets of Langerhans, not in a single gigantic organ, in which the two reciprocal cells interact to each other, and also with an additional cell type, δ cell. We found that the positive/negative interactions between the islet cells are designed not only to reduce the wasteful zero-sum action of glucagon and insulin, but also to enhance/suppress synchronization of hormone secretions between islets under high/normal glucose conditions. Thus we suggest that the anti-symmetric interaction between three cell populations can organize an effective network motif for controlling network synchronization.
Living systems maintain internal homeostasis against external perturbations (1). The endocrine system orchestrates the dynamic equilibrium via long-distance messengers, hormones. Most physiological processes are controlled by negative feedback and antagonistic pairs of hormones, e.g., insulin/glucagon for glucose homeostasis (2), calcitonin/parathyrin for calcium homeostasis (3), and leptin/ghrelin for energy homeostasis (4). As the sustainability of life represents rhythmic oscillation, neither to be extinction nor explosion, hormones also have temporal oscillations (5, 6). A fundamental question is why hormones broadcast information through waves like electrical transmission. In principle, both amplitude and phase of waves can encode information. In addition to the amplitude modulation, the relative phase coordination between different hormones, and the phase synchronization between different sources (cells or tissues) of the same hormones should have functional implications. To explore the evidence of phase modulation, we especially focus on glucose homeostasis, one of the most well studied subjects due to diabetes research.

Glucose, a primary energy source in the body, is mainly regulated by insulin and glucagon secreted by β and α cells in the pancreas. They are clustered together with an additional cell type, δ cell, to form a micro-organ, the islet of Langerhans. Several millions of islets are scattered in the human pancreas. For the effective regulation of glucose homeostasis, special coordination between insulin and glucagon pulses and between different islets is expected. The out-of-phase coordination of insulin and glucagon pulses has been observed in vitro (7) and in vivo experiments (8). The coordination implies the interaction between islet cells. Indeed, it has long been observed that α cells have positive interactions to β and δ cells, while δ cells have negative interactions to α and β cells (9). Furthermore, β cells have a negative interaction to α cells, but a positive one to δ cells, which is the last piece of interaction recently confirmed (10). It is a long standing puzzle why they interact this way as a whole (11)? Another important coordination is the synchronization between islets. It has been implicitly assumed that islets are always synchronized to produce oscillatory hormone profiles in blood. Otherwise, the hormone profile secreted by millions of islets would be flat. However, this assumption is recently reconsidered by raising the possibility that every islet is not functionally identical (12).
Here we model the network of islet cells and examine how uniquely the native network can coordinate phases between insulin and glucagon, and between islets. Then we demonstrate that the native network of the anti-symmetric interactions between islet cells is special for controlling synchronization between islets.

**Intra-islet network and glucose homeostasis**

Endocrine $\alpha$, $\beta$, and $\delta$ cells generate pulses of glucagon, insulin, and somatostatin, respectively. The spontaneous hormone oscillations can be described by amplitude and phase of a generic oscillator:

\[
\begin{align*}
\dot{r}_{n\sigma} &= [f_{\sigma}(G) - r_{n\sigma}^2] r_{n\sigma}, \quad (1) \\
\dot{\theta}_{n\sigma} &= \omega_{n\sigma} - g_{\sigma}(G) \cos \theta_{n\sigma} \quad (2)
\end{align*}
\]

for the cell type $\sigma \in \{\alpha, \beta, \delta\}$ in the $n$th islet. The differential equations generate oscillations with a stationary amplitude $r_{n\sigma} = \sqrt{f_{\sigma}}$ and an intrinsic phase velocity $\dot{\theta}_{n\sigma} = \omega_{n\sigma}$. We focus on slow hormone oscillation with a period of $\omega_{n\alpha}^{-1} = 5 \pm 1$ minutes (2). Given amplitude and phase, the hormone secretion from the $\sigma$ cell in the $n$th islet is defined as $H_{n\sigma} \equiv r_{n\sigma} (\cos \theta_{n\sigma} + 1)$, where the phase $\theta_{n\sigma} = 0$ and $\pi$ represents maximal and basal secretion, respectively. Note that a unity is introduced to prevent negativity of hormone secretion. The amplitude modulation $f_{\sigma}(G)$ depends on glucose concentration $G$. Briefly $f_{\alpha}$ and $f_{\beta}$ are decreasing and increasing functions for $G$, since $\alpha$ cells secrete glucagon at low glucose, while $\beta$ cells secrete insulin at high glucose. Furthermore, the phase modulation $g_{\alpha}(G)$ is introduced to consider that the hormone pulses are not pure sine waves. They modulate the duration of active and silent phases depending on glucose concentration [See Section 1 in Supplementary Material for the details of $f_{\sigma}(G)$ and $g_{\sigma}(G)$].

Each islet responds to a global glucose concentration $G$, and secretes hormone accordingly (Fig. 1A). The total glucagon $NH_{\alpha} = \sum_{n=1}^{N} H_{n\alpha}$ from $N$ islets contributes to increase $G$ by stimulating
the breakdown of glycogen into glucose in the liver, while the total insulin \( NH_\beta = \sum_{n=1}^{N} H_{n\beta} \) contributes to decrease \( G \) by synthesizing glycogen from glucose in the liver and clearing glucose into peripheral tissues. Here unlike the positive flux for glucose, the negative flux is proportional to the present glucose concentration. The following equation summarizes the glucose regulation:

\[
\dot{G} = \lambda N(G_0 H_\alpha - G H_\beta) + I(t),
\]

where \( \lambda \) represents the effectiveness of hormone actions for glucose regulation, and \( I(t) \) represents external glucose inputs reflecting food intake (positive flux) or exercise (negative flux). Finally, we balance the glucagon and insulin action at a normal glucose concentration \( G_0 \).

Given positive/negative glucose inputs \( I(t) \), typical dynamics of glucose and hormones are shown in Fig. 1B. This is a mean field model where each islet does not interact to each other, but total hormones secreted by them affect the glucose, which then affects reversely to each islet. Thus individual islets interact indirectly through the global glucose. Here the glucose, regulated by the spontaneous hormone oscillations, is also oscillating. The glucose oscillation can contribute to entrain islets to have similar phases, which is called glucose entrainment (13).

Now we consider the intra-islet interaction between \( \alpha, \beta, \) and \( \delta \) cells, and their roles for regulating glucose homeostasis. First, by using a complex variable \( Z_{n\sigma} = r_{n\sigma} e^{i \theta_{n\sigma}} \), we combine the amplitude and phase dynamics in Eqs. (1) and (2):

\[
\dot{Z}_{n\sigma} = J_{n\sigma} Z_{n\sigma} + \sum_{\sigma'} A_{\sigma\sigma'} Z_{n\sigma'},
\]

where \( J_{n\sigma} = f_{\sigma} Z_{n\sigma}^* + i \omega_{n\sigma} - i g_{n\sigma} (Z_{n\sigma} + Z_{n\sigma}^*) / \sqrt{4 Z_{n\sigma} Z_{n\sigma}^*} \) and the complex conjugate \( Z_{n\sigma}^* \) of \( Z_{n\sigma} \).

Then, in the presence of the intra-islet interaction, the islet model is written as

\[
\dot{Z}_{n\sigma} = J_{n\sigma} Z_{n\sigma} + K \sum_{\sigma'} A_{\sigma\sigma'} Z_{n\sigma'},
\]

where \( K \) represents the interaction strength, and adjacent matrix \( A_{\sigma\sigma'} \) represents interaction signs from \( \sigma' \) cell to \( \sigma \) cell within each islet. Positive/negative interaction leads the amplitude and phase of \( \sigma \) cell to be close/away to the amplitude and phase of \( \sigma' \) cell. Ignoring self interactions ( \( A_{\sigma\sigma} = 0 \) ), total 729 (=3^6) networks are possible with either positive, none, or
negative interaction for each link (Fig. 1C). Then we conducted the glucose regulation simulations with various glucose stimuli \( I \), and obtained the corresponding glucose level, and glucagon and insulin secretions for all the possible networks (Fig. 1D). All the networks could reasonably control the glucose stimuli by balancing the antagonistic hormones, glucagon and insulin. Interestingly, the native network 121212 emerges as one of efficient networks that consume hormones minimally for the glucose regulation [See Section 2 in Supplementary Material for the parameter independence of our conclusion].

**Effective networks for minimal hormone consumptions**

In the glucose regulation balanced by glucagon and insulin, their wasteful zero-sum is possible. Thus we calculated hormone consumption \( H = H_\alpha + H_\beta \) at normal (\( I = 0 \)) and high (\( I = 2G_0 \)) glucose conditions (Fig. 2A). Since \( \alpha \) and \( \beta \) cells are key components for the glucose regulation, first we focus on the mutual interaction between them: (i) mutual activation networks (11xxxx); (ii) mutual inhibition networks (22xxxx); (iii) native asymmetric networks (12xxxx); (iv) inverse asymmetric networks (21xxxx). Here the mutual activation/inhibition networks generally consume larger amount of hormones because the mutual interaction has the same sign, and construct positive feedback loops, \( \alpha \rightarrow \beta \rightarrow \alpha \) and \( \beta \rightarrow \alpha \rightarrow \beta \), regardless of signs (positive/negative). The mutual activation/inhibition networks have positive coupling terms, \( A_{\alpha\beta} \cos(\theta_{n\beta} - \theta_{n\alpha}) \) and \( A_{\beta\alpha} \cos(\theta_{n\alpha} - \theta_{n\beta}) \) in the amplitude part of Eq. (4), which increase both amplitudes \( r_{n\alpha} \) and \( r_{n\beta} \). Among asymmetric networks, 12xxxx networks consume less hormones than 21xxxx networks at high glucose, because \( \alpha/\beta \) cells are successfully suppressed/enhanced to decrease glucose levels.

Next we checked the robustness of glucose regulation by quantifying fluctuations of glucose concentration at normal and high glucose conditions (Fig. 2B). In general, glucose oscillations can entrain islets to follow the same rhythm. The glucose entrainment may cause concentration of hormone pulses from synchronized islets, and the hormone amplification may result in large fluctuations for glucose regulation. Thus a strong correlation is expected between the glucose fluctuations (Fig. 2B) and inter-islet synchronization (Fig. 2C). Here to quantify synchronization,
we adopted the usual synchronization index for oscillators, \( \rho_\sigma e^{i\Theta_\sigma} = N^{-1} \sum_{n=1}^{N} e^{i\theta_n} \), where \( \rho_\sigma \) measures the degree of synchronization (1 for perfect synchronization and 0 for complete desynchronization), and \( \Theta_\sigma \) captures average phase for \( \sigma \) cells. In general, 11xxxx networks show small glucose fluctuations and low inter-islet synchronization, while 22xxxx networks show large glucose fluctuations and high inter-islet synchronization. The mutual activation networks have frustration for the coordination between \( \alpha \) and \( \beta \) cells: the (internal) mutual positive interactions lead them to have in-phase coordination, while the (external) glucose lead them to have out-of-phase coordination. The frustration hinders different islets from generating coherent behavior under the glucose entrainment. On the other hand, the mutual inhibition networks lack the frustration, and then every islet is easily entrained to the external glucose with out-of-phase coordination between \( \alpha \) and \( \beta \) cells.

The strong correlation between glucose fluctuations and inter-islet synchronization is exempt in networks 12xxxx. They show desynchronization at normal glucose, but synchronization at high glucose. At normal glucose, small glucose fluctuations seem natural with low inter-islet synchronization. At high glucose, large glucose fluctuations are expected with high inter-islet synchronization because the concentrated hormone pulses from synchronized islets cause large fluctuations in glucose regulation in Eq. (3). Furthermore, the out-of-phase coordination between \( H_\alpha \) and \( H_\beta \) can amplify the fluctuation. However, some networks including the native network 121212 show small glucose fluctuations with high inter-islet synchronization. This counter-intuitive small glucose fluctuation is outcome of avoiding the out-of-phase effect by tuning the phase coordination between \( G \) and \( H_\beta \) to make \( H_\alpha \) and \( GH_\beta \) uncoordinated. Then \( \dot{G} \) can stay negligible at stationary states.

Effective homeostatic networks should tightly regulate glucose levels with small fluctuations by consuming minimal amount of hormones. Among total 729 possible networks, we sorted out the effective networks that consume less amounts of hormones than network 000000 (no interaction between islet cells), and show small glucose fluctuations (\( \delta G / G < 0.1 \)) (Fig. 2D). The criteria identified ten effective networks (Fig. 2E; See Section 3 in Supplementary Material). Indeed they
are subsets or transformations of network 121212 or 12212. In other words, if one removes some links or change cell names from 121212 or 122212, one can have the remaining eight networks. We noticed that the asymmetric interactions between α and β, and between β and δ cells are, not always, but well conserved in the effective networks. Furthermore, mutual activation/inhibition between any cell pairs never happens. Networks 121212 and 122212 are topologically distinct. Network 121212 has distinguishable cells: one cell suppresses the other two; one cell enhances the other two; and one cell suppresses one and enhances one. However, network 122212 has indistinguishable cells: every cell suppresses and enhances the others. In other words, if one hide cell names, one cannot distinguish cells.

Controlling inter-islet synchronization

The effective networks have a special feature of controllable inter-islet synchronization depending on glucose conditions. In contrast, the network 000000 (no interaction between islet cells) has a serious problem that islets are easily entrained to glucose oscillation and synchronized to each other (Fig. 3A). Then the synchronized hormone secretion amplifies glucose fluctuations. On the other hand, networks 121212 and 122112 tightly regulate minimal glucose fluctuations especially at normal glucose. We then asked how the effective networks can control the inter-islet synchronization.

We found that network 121212 and 122112 have different numbers of attractors in the phase dynamics in Eq. (4) under different glucose conditions. They have triple attractors of phase difference \((\theta_\alpha - \theta_\beta, \theta_\alpha - \theta_\delta)\) at normal glucose, while the distinction vanishes at high glucose (Fig. 3B and 3C; See Section 4 in Supplementary Material for the analysis). Thus different islets sit on different attractors at normal glucose. This makes different islets to have different phase coordination between islet cells. Then the heterogeneous phase coordination hinders islets from being synchronized. At high glucose, however, the triple attractors vanish, and islets do not have clearly distinct phase coordination between islet cells. They show out-of-phase coordination between α and β cells, which is consistent with experimental observations (7, 8). Then, islets become easily synchronized without resistance to the glucose entrainment. This scenario is
exactly the same under low glucose conditions (See Section 5 in Supplementary Material).
Unlike those effective networks, network 00000 has no distinct attractors regardless of glucose conditions (Fig. 3D), and glucose oscillations can easily entrain islets to be synchronized. Therefore, we conclude that the inter-islet desynchronization at normal glucose is an active process resistant to glucose entrainment by generating multiple attractors in dynamics. We also confirmed the controllability of inter-islet synchronization in the population model where each islet is composed of populations of islet cells (See Section 6 in Supplementary Material).

**Conclusion**

Here we have revealed the link between the intra-islet network and the inter-islet synchronization, both of which have been two long-standing puzzles in islet biology. First, the anti-symmetric interactions between α, β, and δ cells are special to prevent the wasteful zero-sum actions of glucagon and insulin for glucose regulation. More importantly, the intra-islet network contributes to control the synchronization between islets in the pancreas. Since human pancreas has several millions of islets, instead of a single gigantic organ like the brain, lung, and heart, the (de)synchronization of their hormone secretion have huge impacts on human physiology. The multiplicity allows signal amplification and suppression, once the coherence of the multiple islets is controllable. This study has demonstrated the potential of phase modulation in biological oscillations.

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**Fig. 1. Glucose regulation and islet-cell network.** (A) Schematic diagram of glucose regulation by pancreatic islets. Endocrine α, β, and δ cells in the pancreatic islets monitor and regulate blood glucose concentration $G$, perturbed by external input $I$. Glucagon $H_\alpha$ secreted by α cells increases $G$, while insulin $H_\beta$ secreted by β cells decreases $G$. (B) Given external glucose input $I(t)$ (red line in upper plot), glucose $G$ (solid black line) is regulated by two counter-regulating hormones, $H_\alpha$ (red line in lower plot) and $H_\beta$ (green line). Note that $G_0$ is a normal glucose concentration in the absence of input ($I = 0$). (C) Network annotation for describing the interactions between islet cells. The interaction signs of $A_{\beta\alpha}$, $A_{\alpha\gamma}$, $A_{\delta\alpha}$, $A_{\alpha\delta}$, $A_{\delta\beta}$, and $A_{\beta\delta}$ can take either none (0), positive (1), or negative (2) values. Following this notation, the network 121212 represents the native network of islet cells. (D) Stationary glucose concentration and corresponding hormone consumptions for various external glucose inputs. Negative/positive inputs $I$ induce low/high glucose conditions. Total 729 networks are considered: network 121212 (red) and the other networks (gray). See Section 2 in Supplementary Material for the details of the model and standard parameter values.
Fig. 2. Efficient hormone consumption and glucose regulation. (A) Hormone consumption $H = H_\alpha + H_\beta$ of 729 networks at normal ($I = 0$) and high ($I = 2G_0$) glucose conditions: network 121212 (pink triangle, native interaction between islet cells), 000000 (purple inverted triangle, no interaction), 11xxxx (red circles, mutual activation between $\alpha$ and $\beta$ cells), 12xxxx (green circles, native asymmetric interaction), 21xxxx (cyan circles, inverse asymmetric interaction), 22xxxx (blue circles, mutual inhibition), and the others (gray circles). Network 000000 is located at the crossing of vertical and horizontal black lines. (B) Temporal fluctuations of glucose, normalized by absolute glucose concentration, $\delta G = \Delta G / G$ at the normal/high glucose conditions. Black lines separate the networks that produce small glucose fluctuations ($\bar{\delta G}_{\text{normal}}^2 + \bar{\delta G}_{\text{high}}^2 < 0.1^2$). (C) Degree of synchronization between islets at the normal/high glucose conditions. The synchronization index is an average index $\rho = (\rho_\alpha + \rho_\beta + \rho_\delta) / 3$ of $\alpha$, $\beta$, and $\delta$ cells: $\rho = 1/0$ represents perfect synchronization/independence between islets. (D) Ten effective networks satisfy two criteria of minimal hormone consumption and small glucose fluctuations inside the black lines in (A) and (B). (E) Topologies of the ten effective networks with their annotations. Positive/negative interactions are represented by red/blue bar-headed arrows, respectively. Black rectangle groups subsets and transformations of network 121212, while red rectangle groups subsets of network 121221.
Fig. 3. Controllable inter-islet synchronization and phase coordination between islet cells. (A) Glucose regulation and inter-islet synchronization for network 121212 (red), network 122112 (blue) and 000000 (black), given external glucose input ($G = 2G_0$) during $100 < t < 160$. Phase snapshots of $\alpha$, $\beta$, and $\delta$ cells under different glucose conditions (regimes I, II, and III) for (B) network 121212, (C) 122112, and (D) 000000. Upper panel: absolute phases ($\theta_{\alpha\alpha} - \theta_{\alpha\beta}$, $\theta_{\beta\beta}$, $\theta_{\delta\delta}$) of $\alpha$ (red), $\beta$ (green), and $\delta$ (blue) cells in 200 islets. Lower panel: phase differences ($\theta_{\alpha\alpha} - \theta_{\alpha\beta}$, $\theta_{\beta\beta} - \theta_{\delta\delta}$).
Supplementary Materials

Phase Modulation of Hormonal Oscillations

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1. Islet model
We describe the detailed islet model in the presence of intra-islet interaction. The amplitude and phase dynamics in Eq. (4) are

\[
\dot{r}_{\sigma} = \left[f_{\sigma}(G) - r^2_{\sigma}\right] r_{\sigma} + K \sum_{\alpha} A_{\alpha\sigma} \cos(\theta_{\alpha\sigma} - \theta_{\sigma}), \quad \text{(S1)}
\]

\[
\dot{\theta}_{\sigma} = \omega_{\sigma} - g_{\sigma}(G) \cos\theta_{\sigma} + K \sum_{\alpha} A_{\alpha\sigma} \sin(\theta_{\alpha\sigma} - \theta_{\sigma}). \quad \text{(S2)}
\]

Each cell has heterogeneous intrinsic phase velocities $\omega_{\sigma}$ that follows a Gaussian distribution with mean 5 min$^{-1}$ and standard deviation 0.1 min$^{-1}$. The islet model considers amplitude and phase modulations by glucose concentration. First, the amplitude modulation controls glucose-dependent hormone secretions of $\alpha$, $\beta$, and $\delta$ cells (Fig. S1):

where \( G_0 = 7 \text{ mM}, \Delta G_0 = 2 \text{ mM}, \) and \( a_\delta = 0.5 \). The amplitude modulations are based on the observed glucose dose response of insulin, glucagon, and somatostatin secretions \((I)\). The somatostatin secretion of \( \delta \) cells has a lower glucose threshold than the insulin secretion. In addition, we parameterize the lower fraction of \( \delta \) cells \(( a_\delta < 1)\), compared with two major populations of \( \alpha \) and \( \beta \) cells.

\[
f_\alpha(G) = \frac{1}{2} \left[ 1 - \tanh \left( \frac{G - G_0}{5} \right) \right], \quad (S3)
\]
\[
f_\beta(G) = \frac{1}{2} \left[ 1 + \tanh \left( \frac{G - G_0}{5} \right) \right], \quad (S4)
\]
\[
f_\delta(G) = \frac{a_\delta}{2} \left[ 1 + \tanh \left( \frac{G - G_0 + \Delta G_0}{5} \right) \right], \quad (S5)
\]

Second, the phase modulation controls the duration of active/silent phases in the hormone pulses:

\[
g_\alpha(G) = \mu(G - G_0), \quad (S6)
\]
\[
g_\beta(G) = \mu(G_0 - G), \quad (S7)
\]
\[
g_\delta(G) = \mu(G_0 - G). \quad (S8)
\]

These phase modulations lead \( \alpha \) cells to have longer active phases at low glucose \(( G < G_0 )\) and \( \beta \) and \( \delta \) to have longer active phases at high glucose \(( G > G_0 )\). The glucose-dependent pulse shapes

**Fig. S1. Glucose-dependent amplitude modulation.** \( \alpha \) cells \(( f_\alpha, \text{ red})\), \( \beta \) cells \(( f_\beta, \text{ green})\), and \( \delta \) cells \(( f_\delta, \text{ blue})\).
for β cells (Fig. S2) are consistent with experimental observations (2). These descriptions complete the amplitude and phase dynamics in Eq. (4).

![Graph](image)

**Fig. S2. Phase modulation.** Glucose-dependent pulse shapes of insulin from a single β cell for various external glucose inputs.

One technical note is that since the negative amplitude \( r_{\alpha} = -\sqrt{f_{\alpha}} \) is another approximate solution of Eq. (S1), we avoid the negative amplitude by transforming as \( r_{\alpha} \rightarrow -r_{\alpha} \) and \( \theta_{\alpha} \rightarrow \theta_{\alpha} + \pi \) whenever the negative one is confronted in simulations.

### 2. Parameter dependence of the islet model

Although we formulate the islet model constrained by experimental observations, we still lack exact information on parameter values. Thus we check their dependences of our conclusions.

Note that our standard parameter values are \( K = 0.4, \mu = 0.1, a = 0.5, \lambda = 1 \), and \( N=200 \).

1. Intra-islet coupling strength, \( K \)

   Too small \( K \) cannot distinguish the topological difference between islet-cell networks, while too strong \( K \) induces strong nonlinear effects on the phase dynamics in Eq. (S2), and perturbs the principal spontaneous oscillations governed by intrinsic frequency \( \omega_{\alpha} \). If \( K \) is sufficiently large
(\(K > 0.4\)), the native network 121212 shows robust characteristics of small hormone consumption and small glucose fluctuations (Fig. S3).

**Fig. S3. Intra-islet coupling strength.** Hormone consumption of 729 networks at normal (\(I = 0\)) and high (\(I = 0.5G_0\)) glucose conditions (A), and the temporal fluctuations of glucose (B) under various intra-islet coupling strengths, \(K = 0.1, 0.3, \) and \(0.6\), from left to right. The colors and notations are the same as Fig. 2.

(2) Pinning strength, \(\mu\)

The phase modulation through a pinning term in Eq. (S2) captures the glucose-dependent shapes of hormone pulses. Thus the pinning term represents the response of islets to glucose perturbations. The oscillatory glucose changes are then able to entrain islets to be synchronized. Here too weak pinning cannot induce the inter-islet synchronization, while too strong pinning (\(|\mu| > \omega_n\)) stop islet cells oscillating by being stuck at \(\theta_n = \cos^{-1}(\omega_n/\mu)\). At a lower pinning
strength, network 000000 (no interaction between islet cells) starts to show inter-islet synchronization, compared with network 121212 (Fig. S4). In addition, given pinning strength (0.07 < µ < 0.2), network 121212 generates different degrees of inter-islet synchronization for different external glucose inputs \( I \). Mean glucose concentration \( \bar{G} \) is independent on the pinning strength, but glucose fluctuations are highly correlated with inter-islet synchronization.

![Image](image)

**Fig. S4. Pinning strength.** Inter-islet synchronization index \( \rho \) for networks (A) 000000 and (B) 121212 under external glucose inputs \( I = 0 \) (black), \( I = 0.5G_0 \) (red), and \( I = 2G_0 \) (green). (C) Mean glucose concentration \( \bar{G} \) for networks 000000 (black) and 121212 (red) under a normal glucose condition (\( I = 0 \)). Error bars represent standard deviation.

(3) Amplitude of \( \delta \) cells, \( a_\delta \)

Considering the minority of \( \delta \)-cell populations, the value of \( a_\delta \) is expected to be \( 0 < a_\delta < 1 \).

Glucose, hormone, and inter-islet synchronization profiles do not depend much on its variations (Fig. S5). Two extreme networks 120000 and 000202 correspond to the ignorance (\( a_\delta = 0 \)) and emphasis (\( a_\delta > 1 \)) of the interactions from \( \delta \) cells.
**Fig. S5. Effect of δ-cell amplitude.** (A) Two extreme networks: 120000 and 000202, ignoring and emphasizing interactions from δ cells, compared with the native islet network 121212. (B) Time traces of glucose, hormones, and inter-islet synchronization indices under a glucose stimulus \( I = 2G_0 \) for \( 200 < \text{Time} < 260 \). Red-dotted box represents the results of network 121212 for \( a_δ = 0.1, 0.5, 1, \) and 2 from left to right. The leftmost column is the result of network 120000, and the rightmost column is the result of network 000202.

(4) Hormone effectiveness, \( \lambda \)

Too small \( \lambda \) fails to effectively regulate glucose in Eq. (2), while too large \( \lambda \) leads \( G \) largely fluctuating (Fig. S6). Furthermore, larger \( \lambda \) diminishes the relative contribution of external glucose inputs \( I \) in Eq. (2).
**Fig. S6. Hormone effectiveness for glucose regulation.** Time traces of glucose concentration (upper) and hormones (lower) with various hormone effectiveness parameter, $\lambda / N = 0.1, 0.5, 1, \text{ and } 10$, from left to right under a glucose stimulus $I = 2G_0$ for $200 < \text{Time} < 260$.

(5) Total islet number, $N$

As $N$ increases, the glucose regulation becomes less fluctuating (Fig. S7). In addition, the initial condition dependence of the nonlinear dynamics is largely suppressed in the large $N$ limit. For the analysis, we rule out the capacity increase of hormone secretions due to larger $N$ by normalizing the hormone effectiveness ($\lambda / N = 0.5$).
Fig. S7. Effects of islet number. (A) Temporal glucose profiles under a glucose stimulus ($I = 0.5G_0$) for Time > 200: $N = 10$ (black), 100 (red), and 1000 (green). (B) Temporal fluctuations of glucose concentration for various islet numbers before (black) and after (red) the glucose stimulus. Given the same protocol, (C) inter-islet synchronization index for $\beta$ cells, and (D) its fluctuations. Dotted lines are drawn for guiding eyes.

(6) Time delay of hormone actions, $\tau$

It takes time for the hormones, secreted by the pancreas, to act on the liver or peripheral tissues. The time delay can be simply considered by reformulating Eq. (2) as

$$\dot{G} = \lambda(G_0H'_\alpha - GH'_\beta) + I(t) ,$$  \hspace{1cm} (S9)

$$\tau H'_\alpha = H'_\alpha - H_\alpha .$$  \hspace{1cm} (S10)

The time delay $\tau$ may have a time scale of 1 minute, considering the circulation time of the blood in the body. Such a short delay does not affect the glucose regulation (Fig. S8).
Fig. S8. Time traces of glucose, hormones, and degree of synchronization under time delays. $\tau=0, 1, 10, 100$ min from left.

### 3. Optimal networks for glucose homeostasis

Among 729 networks, we identified top ten intra-islet networks (Table S1) that consume small amount of hormones but tightly regulate glucose with small fluctuations.

**Table S1.** Hormone consumption, glucose fluctuation, and inter-islet synchronization of ten effective networks.

| #   | Network | $H_{\text{normal}}$ | $H_{\text{high}}$ | $\bar{G}_{\text{normal}}$ | $\bar{G}_{\text{high}}$ | $\rho_{\text{normal}}$ | $\rho_{\text{high}}$ |
|-----|---------|----------------------|-------------------|--------------------------|------------------------|------------------------|------------------------|
| 1   | 000012  | 1.357                | 1.288             | 0.048                    | 0.052                  | 0.089                  | 0.319                  |
| 2   | 011212  | 1.292                | 1.351             | 0.012                    | 0.048                  | 0.065                  | 0.335                  |
| 3   | 202012  | 1.329                | 1.299             | 0.039                    | 0.040                  | 0.116                  | 0.309                  |
4. Phase plane analysis for phase attractors

To understand the attractors of phase dynamics, we consider Eq. (S2) in a simplified setting in which the intrinsic angular velocities are identical ($\omega_{\alpha} = \omega$) and the pinning term is off ($\mu = 0$). Note that the pinning term naturally becomes zero at normal glucose ($G = G_0$) in Eqs. (S6-8). Then the phase equations are

$$\dot{\theta}_\alpha = -K \frac{r_\beta}{r_\alpha} \sin(\theta_\beta - \theta_\alpha) - K \frac{r_\delta}{r_\alpha} \sin(\theta_\delta - \theta_\alpha), \quad (S12)$$

$$\dot{\theta}_\beta = K \frac{r_\alpha}{r_\beta} \sin(\theta_\alpha - \theta_\beta) - K \frac{r_\delta}{r_\beta} \sin(\theta_\delta - \theta_\beta), \quad (S13)$$

$$\dot{\theta}_\delta = K \frac{r_\alpha}{r_\delta} \sin(\theta_\alpha - \theta_\delta) + K \frac{r_\beta}{r_\delta} \sin(\theta_\beta - \theta_\delta). \quad (S14)$$

Since we are interested in the phase differences between $\alpha$, $\beta$, and $\delta$ cells, relative phases, $x = \theta_\alpha - \theta_\beta$ and $y = \theta_\alpha - \theta_\delta$, can be defined. Using Eqs. (S12-14), we obtain

$$\dot{x} = K \left[ \frac{r_\beta}{r_\alpha} - \frac{r_\alpha}{r_\beta} \right] \sin x + K \frac{r_\beta}{r_\alpha} \sin y + K \frac{r_\alpha}{r_\beta} \sin(x - y), \quad (S15)$$

$$\dot{y} = K \frac{r_\beta}{r_\alpha} \sin x + \left[ \frac{r_\delta}{r_\alpha} - \frac{r_\alpha}{r_\delta} \right] \sin y + K \frac{r_\delta}{r_\alpha} \sin(x - y). \quad (S16)$$

Depending on the amplitudes $r_\alpha$, different phase dynamics emerges. Approximately, $r_\alpha > r_\beta$, $r_\delta$ at low glucose, $r_\beta > r_\alpha$, $r_\delta$ at high glucose, and $r_\alpha = r_\beta = r_\delta$ at normal glucose. Under the glucose conditions, the phase dynamics have single and triple attractors at low/high and normal glucose (Fig. S9).
Fig. S9. Vector flows in phase dynamics. (A, D) \( r_\alpha = 1 \), \( r_\beta = r_\delta = 0.2 \), (B, E) \( r_\beta = 1 \), \( r_\alpha = r_\delta = 0.2 \), (C, F) \( r_\alpha = r_\beta = r_\delta = 1 \) for network 121212 (A, B, C) and network 122112 (D, E, F).

5. Low glucose challenge
Pancreatic islets regulate not only for high glucose, but also for low glucose. Therefore we also challenged islets by lowering glucose concentration with negative glucose influx \( \beta < 0 \). The controllable inter-islet synchronization emerges at low glucose (Fig. S10).
Fig. S10. Controllable inter-islet synchronization and phase coordination between islet cells. (A) Glucose regulation and inter-islet synchronization for network 121212 (red), network 122112 (blue) and 000000 (black), given external glucose input \( I = -0.5G_0 \) during \( 100 < t < 160 \). Phase snapshots of \( \alpha \), \( \beta \), and \( \delta \) cells under different glucose conditions (regimes I, II, and III) for (B) network 121212, (C) 122112, and (D) 000000. Upper panel: absolute phases \( (\theta_\alpha, \theta_\beta, \theta_\delta) \) of \( \alpha \) (red), \( \beta \) (green), and \( \delta \) (blue) cells in 200 islets. Lower panel: phase differences \( (\theta_\alpha - \theta_\delta, \theta_\beta - \theta_\delta) \).

6. Population model
Real islets are composed of populations of islet cells, not single \( \alpha \), \( \beta \), and \( \delta \) cells within each islet. Therefore, we consider populations of islet cells with known compositions and organization \((\mathcal{J})\). In the population model, each cell has different nearest neighbors. The interaction follows exactly the same as the single cell model, but here one has to consider autocrine interaction that
the same cell types interact to the same cell types. We used positive autocrine interactions as considered in the previous study (4). We confirmed that the controllable synchronization is also realized in the population model (Fig. S11).

Fig. S11. Population model and controllable synchronization. Total 1000 islets in which 1357 cells (30% α, 60% β, and 10% δ cells) are organized with a partial mixing structure. Glucose is then regulated by 1000×1357 islet cells under a glucose stimulus (\( I = 3G_0 \)) for 300 < Time < 360. Corresponding hormone secretions and degree of synchronization between α cells in the pancreas, and between β cells in the pancreas.

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