

Autopoietic Influence Hierarchies in Pancreatic β CellsDean Korošak,^{1,2} Marko Jusup³, Boris Podobnik,^{4,5,6,7,8} Andraž Stožer,¹ Jurij Dolensek,^{1,9}
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β cells are biologically essential for humans and other vertebrates. Because their functionality arises from cell-cell interactions, they are also a model system for collective organization among cells. There are currently two contradictory pictures of this organization: the hub-cell idea pointing at leaders who coordinate the others, and the electrophysiological theory describing all cells as equal. We use new data and computational modeling to reconcile these pictures. We find via a network representation of interacting β cells that leaders emerge naturally (confirming the hub-cell idea), yet all cells can take the hub role following a perturbation (in line with electrophysiology).

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The importance of the nutrient-sensing and insulin-secreting β cells in vertebrates is hard to overstate. These cells reside in pancreatic islets, where they extensively communicate with each other and their environment [1]. The intercellular communication, in particular, serves to coordinate and synchronize cellular operations through which insulin is released in proportion to stimulation and metabolic requirements [2,3]. The delicate nature of this task is reflected in the continual need to prevent over-secretion, and subsequent hypoglycemia [4], despite intracellular stores holding sufficient insulin to exceed the lethal dose by orders of magnitude if released at once.

On a microscopic scale, β cells are electrically and metabolically coupled via gap junctions built from the protein connexin-36 (Cx36) [5]. The key role of such coupling is seen in the fact that the loss of Cx36 channels has a detrimental impact on β -cell cooperation [6,7], leading to uncoordinated plasma depolarizations, the desynchronization of calcium signals, and increases in basal insulin release. Sufficient Cx36 coupling, by contrast, curbs the β -cell intrinsic heterogeneity in glucose sensitivity [8], and in mouse islets, limits the threshold for stimulatory glucose concentration [7] to a narrow band around ≈ 7 mM. Metaphorically, coupled β cells are like individual soldiers who fall in line when the communication channels between them are open. A typical β cell is

coupled to between six and eight neighbors [9,10]. According to electrophysiological theory [11], single cells lack mechanisms to become pacemakers beyond their immediate neighborhood. In terms of our metaphor, there are no generals in the army.

The above-mentioned lateral organization is diametrically opposed to the picture by functional studies of a large number of communicating β cells (referred to as β -cell collectives). For example, intrinsic cellular heterogeneity in glucose sensing [8], heterogeneous gap-junction coupling [12], and extensive paracrine signaling [13] all contribute to an islet-wide complicated cytoplasmic Ca^{2+} dynamics. This dynamics of the Ca^{2+} concentration in the cytosol [14,15] is a key insulin-secretion driver [16]. It has recently become possible to record the Ca^{2+} dynamics with a great spatial and temporal precision using the functional multicellular confocal imaging [17,18]. The high data content of such imaging enables mapping the functional organization of a β -cell collective onto a complex network such that a pair of cells (i.e., network nodes) is linked if the cross-correlation between the corresponding Ca^{2+} signals is large enough [19–24].

Complex-network representations of the functional organization of β -cell collectives (i.e., functional networks) that arise from calcium cross-correlations in intact pancreatic islets reveal a modular structure [25] intertwined with

small-world [20,26] properties. Of particular interest is that some studies [22,24] point to small subsets of highly active β cells whose connectedness and impact on synchronization across islets make these cells candidate leaders. Because of their large degree, we call such candidate leaders *hub cells*. Specifically, the upper 10% of most connected cells are considered hub-cells following [22]. The proponents of the hub-cell idea list many reasons [27] why electrophysiological measurements may have missed detecting hubs. Overall, functional networks suggest that our army of β cells is led by a few generals.

We will hereafter show that the hub-cell idea, rather than contradicting, actually complements electrophysiology. Based on a remarkable agreement between empirical and computational findings, we will argue in favor of an autopoietic influence hierarchy among β cells. Leader cells emerge through cell-cell communication, and thus need not be genetically predisposed for leadership. In the language of the army metaphor, generals do lead, but not by birthright; they get promoted by their peers. Leader cells, furthermore, remain under the radar of electrophysiological measurements by communicating with immediate neighbors just as any other cell would. A direct implication is that a more-or-less arbitrary cell could emerge as a leader, which in turn makes for an ultrarobust architecture of β -cell collectives. Additional wide-reaching implications underpin some of the vital β -cell features.

Methods.—We based our empirical analyses on a dataset obtained via Ca^{2+} imaging of an acutely prepared pancreatic tissue slice [17,28] comprising a rodent oval-shaped islet (approx. dimensions $370 \mu\text{m} \times 200 \mu\text{m}$). Ca^{2+} signals were recorded using a functional multicellular imaging technique at 10 Hz and 256×256 pixel resolution in an 8-bit gray scale color depth. The freely downloadable dataset [29] consisted of 65 536 Ca^{2+} signals, each with 23 873 data points. Our focus was on fast oscillations, which is why all signals were detrended and standardized before use [30].

For the purpose of constructing empirical functional networks, we randomly picked $N = 100$ signals, denoted $x_i(t)$, from the dataset and computed cross-correlations $c_{ij} = [x_i x_j]$, where $[\cdot]$ is a time-averaging operator. The number of data points in each signal was $L = 3 \times 10^3$, corresponding to 5-min exposures of the pancreatic tissue slice to the stimulating glucose concentration of 8 mM. We link two signals i and j in the network if $c_{ij} > c_0$, where c_0 is a threshold selected to give a mean degree $\langle k \rangle = 10$. We have previously shown [31] that the bulk cross-correlation spectrum of typical Ca^{2+} signals follows the predictions of random matrix theory, but the states outside the bulk-spectrum edges carry biological information. The delocalized states corresponding to the largest eigenvalues of the cross-correlation matrix, in particular, were found to harbor contributions from all Ca^{2+} signals, thus revealing an islet-wide collective mode [32].

The computational aspects of the study comprised constructing functional networks from simulated Ca^{2+} signals. Simulations were based on our model [30] that had been found to mimic empirical signals closely. Compared to typical electrophysiological modeling by means of differential-algebraic systems [21], the model's structure is very simple. Each of the $N = 100$ nodes represents a β cell arranged in a random regular network with the degree distribution $P(k) = \delta(k - k_0)$ such that trivially the average node degree is $\langle k \rangle = k_0$. Nodes can change their binary state, corresponding to the calcium activity of individual β cells, from active to inactive or vice versa in two ways. Internal activation is controlled by a forcing parameter f , which is interpretable as the inverse of the glucose concentration to which β cells are exposed. An internally activated node stays in this state over the time period τ_i . External activation is controlled by the state of the k_0 nearest neighbors in conjunction with the coupling strength h , which is interpretable as the intensity of gap-junctional ion exchange. An externally activated node stays in this state over the time period τ_e . The model's behavior is best understood in terms of a compound forcing parameter $f^* = 1 - (1 - f)^{\tau_i} \approx 1 - \exp(-f\tau_i)$ that equals the probability of finding a randomly chosen node internally activated, and an analogous compound coupling parameter $h^* = 1 - (1 - h)^{\tau_e} \approx 1 - \exp(-h\tau_e)$ for external activation. Increasing f^* from 0 to 1 strengthens node activity, at first linearly, and then explosively, where explosiveness is largely determined by the value of the parameter h^* [30]. Such explosive activation of the network corresponds to a β -cell collective exposed to the threshold stimulatory glucose concentration. In simulations we used $k_0 = 10$, $f = 0.28$, $\tau_i = 10$ (giving $f^* \approx 0.96$), and $\tau_e = 1$ (giving $h^* = h$), while the value of h varied as specified in the text. Functional networks were constructed from simulated Ca^{2+} signals in exactly the same way as from empirical ones.

Results.—The degree distributions of empirical and simulated functional networks are practically the same (Fig. 1). We distinguish between two cases. Open symbols pertain to functional networks extracted from empirical data *per se* (squares), and from simulations with strong coupling, $h = 0.8$ (circles). In this case, the obtained degree distributions closely follow a negative binomial distribution $P(k) = \binom{k+r-1}{k} p^k (1-p)^r$, where $p = \langle k \rangle / (r + \langle k \rangle) \approx 0.77$ and $r = 3$ is a numerical parameter. The opposite case, shown using filled symbols, consists of functional networks extracted upon randomizing empirical data (squares) and running simulations with weak coupling, $h = 0.1$ (circles). Both data randomization and weak coupling should produce random functional networks, what indeed transpires given that the obtained degree distributions closely follow a binomial distribution $P(k) = \binom{N}{k} p^k (1-p)^{N-k}$ with $p = \langle k \rangle / N$. The binomial distribution in turn converges to a Poisson distribution $P(k) = \langle k \rangle^k \exp(-\langle k \rangle) / k!$ in the large network limit $N \rightarrow \infty$ when $\langle k \rangle$ is fixed.

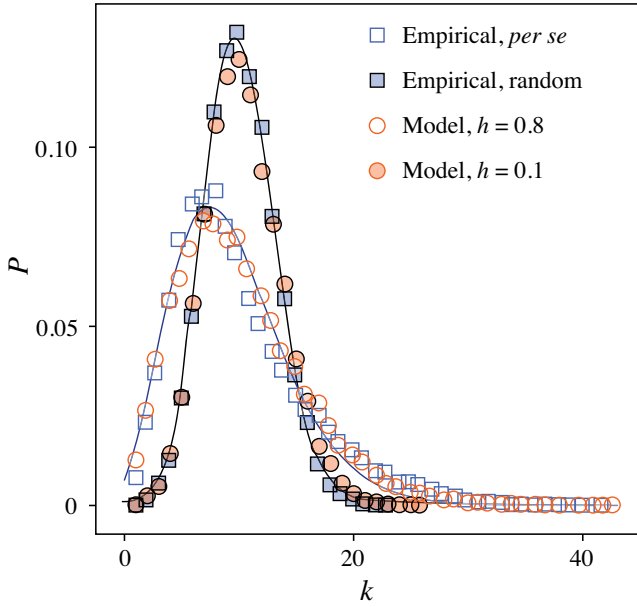


FIG. 1. Functional networks of β cells contain high-degree hubs. The plot shows the configuration-ensemble degree distribution, P , as a function of the node degree, k .

Aside from degree distributions, another informative way of characterizing functional networks is degree correlations, also known as degree assortativity. Reference [33] explains that the elements a_{ij} of a configuration-ensemble adjacency matrix should satisfy the strictly linear relationship $a_{ij} = k_i k_j / \langle k \rangle N$ in zero-assortativity situations. Otherwise, $a_{ij} = (k_i k_j / \langle k \rangle N)^{1+\beta}$, where $\beta < 0$ ($\beta > 0$) indicates negative (positive) assortative mixing. Plots of a_{ij} against $k_i k_j / \langle k \rangle N$ (Fig. 2), while once again revealing an agreement between empirical and simulated functional networks, primarily show that $\beta \approx 0.1$. The degree assortativity of the functional networks is therefore positive, meaning that network nodes are preferentially linked to other nodes of similar degree.

The results so far allow us to estimate the assortativity coefficient of functional networks in an alternative way, which we can then compare with the definition [34,35]; that is, with the degree correlation coefficient between pairs of linked nodes $\rho = (\langle k \rangle \langle k^2 k_{nn} \rangle - \langle k^2 \rangle^2) / (\langle k \rangle \langle k^3 \rangle - \langle k^2 \rangle^2)$, where $k_{nn}^i = k_i^{-1} \sum_j a_{ij} k_j$ is the average degree of the i th node's nearest neighbors. Using the exponent $\beta \approx 0.1 \ll 1$ and the fact that the aforementioned negative binomial distribution converges to a gamma distribution $P(k) = q^{-r} k^{r-1} \exp(-k/q) / \Gamma(r)$ for large $q = \langle k \rangle / r$, the assortativity coefficient is $\rho \approx \beta q^{2\beta} \approx 0.11$ (see Ref. [33]). Following the definition of ρ indeed yields a very similar value (Fig. 3; open symbols for $N_r/N = 0$).

We furthermore tested how two different perturbations [36], signal randomization, and replacement affect the assortativity coefficient. Here, randomization and replacement, respectively, mean that a fraction N_r/N of signals

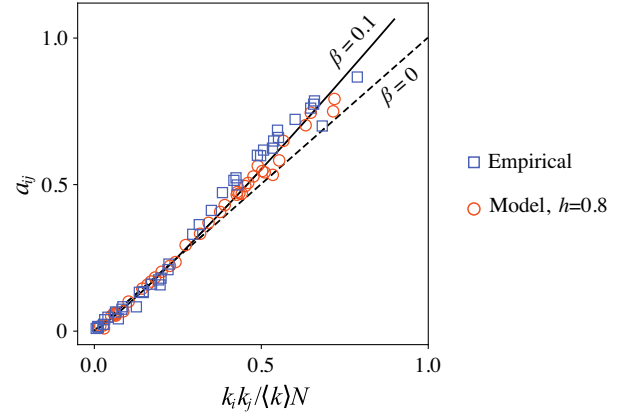


FIG. 2. β -cell functional networks exhibit positive assortative mixing. The plot compares the elements a_{ij} of the configuration-ensemble adjacency matrix against the normalized degree product, $(k_i k_j / \langle k \rangle N)^{1+\beta}$, for two different values of the β exponent, $\beta = 0$ and $\beta = 0.1$.

used in the construction of the original configuration ensemble were either randomly reshuffled or replaced with other random signals from the broader dataset. We found that assortativity of functional networks is robust to random perturbations, but not to perturbations targeting hubs (Fig. 3; open symbols for $N_r/N > 0$). It is therefore hubs that preferentially link to other hubs, which emphasizes their importance in the overall structure of functional networks. Specifically, we are seeing the evidence of a purposeful correlating mechanism at work among β cells because otherwise heterogeneous networks are expected to be disassortative [33,35]. Here, and throughout the rest of the Letter, mentions of heterogeneous networks imply node-degree heterogeneity.

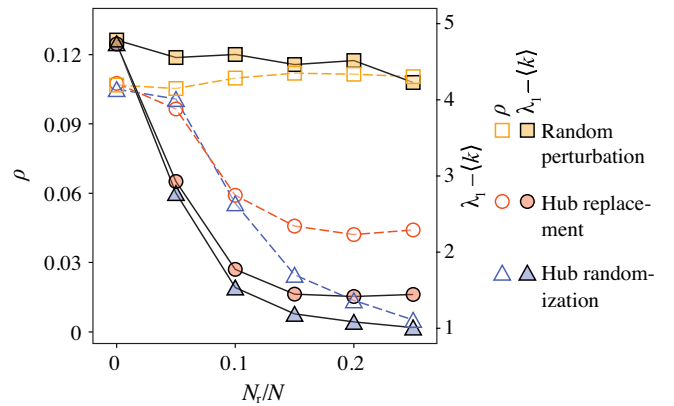


FIG. 3. Assortativity and the largest adjacency-matrix eigenvalue of functional networks are robust to random perturbations, but not to perturbations targeting hubs. The plot shows assortativity, ρ , and the largest eigenvalue of the configuration-ensemble adjacency matrix, λ_1 , (from which the average node degree $\langle k \rangle$ has been subtracted) both as the functions of the fraction of perturbed nodes, N_r/N .

Another measure characterizing a network's structure is the largest eigenvalue of the adjacency matrix, λ_1 . Similarly as with the assortativity coefficient, the value of λ_1 is robust to random perturbations, but not to perturbations targeting hubs (Fig. 3). As progressively more hubs get perturbed, the maximum adjacency-matrix eigenvalue falls to $\lambda_1 = 1 + \langle k \rangle$, which is the value characteristic of random networks with a Poisson degree distribution. This last result reaffirms the importance of hubs for the structure of functional networks and, in turn, hints at an interesting connection with recent experimental findings that generated much excitement.

Experiments show [22,24] that perturbing hub cells can quickly decorrelate a β -cell collective. This implies that hubs carry most of the collective's cross-correlation content, which could be tested using our empirical and simulated Ca^{2+} signals alike. To this end, we employed the pairwise cross-correlations c_{ij} to define $c_i = k_i^{-1} \sum_j a_{ij} c_{ij}$, that is, the i th node's neighborhood-wide average cross-correlation. By pairing the c_i values with the corresponding node degree k_i , we obtained a function $c(k)$. If the β -cell collective's cross-correlation content were equally distributed among all nodes, then we should see $c(k) = \text{const}$, whereas if hubs carried most of the content, then $c(k)$ should be an increasing function of k . We find that the latter is true both for empirical [Fig. 4(a)] and simulated [Fig. 4(b)] Ca^{2+} signals. As with assortativity ρ and the largest eigenvalue λ_1 , random perturbations have little bearing on the function $c(k)$, but targeting high-degree nodes causes decorrelation. With the help of the dynamical network model, we see that perturbing about 10% of hubs is very similar to running simulations with a weak coupling of $h = 0.1$ [Fig. 4(b)].

The model additionally allows us to examine whether the node-degree dependence of the function $c(k)$ could be due to hubs somehow communicating with more of their neighbors than lower-degree nodes. The number of active neighbors (i.e., number of neighbors of a particular node that are in an active state) k^* is, as expected, independent of the degree k when the coupling is weak, $h = 0.1$ [Fig. 4(c)]. The same, however, approximately holds even when the coupling is strong, $h = 0.8$ [Fig. 4(c)]. Because, in the model, all nodes are equal and none of them communicate with an unusual number of neighbors, we are left with a conclusion that the emergence of hubs in functional networks is endogenous to cell-cell communication.

The Supplemental Material [37] provides additional context to the results. Specifically, we discuss in detail the robustness of the results to the topology of underlying networks (SM remark 1), whether underlying-network topology gives any insights into which nodes emerge as hubs in functional networks (SM remark 2), and finally the intransience of hub nodes during a typical postprandial glucose spike (SM remark 3).

Discussion.—Herein, we used a combination of empirical and computational methods to shed new light on, among others, a fundamental tension between electrophysiological theory and the hub-cell idea as it pertains to pancreatic β cells. We started by constructing functional β -cell networks from empirical Ca^{2+} signals, and after that estimated the configuration ensemble [38,39] of such networks. Meanwhile, we also simulated fast β -cell activity using a dynamical network model [40,41] whose outputs faithfully mimic the properties of said empirical Ca^{2+} signals [30]. Upon repeating the construction of functional networks, but now from simulated signals, we found remarkable quantitative agreement between the results.

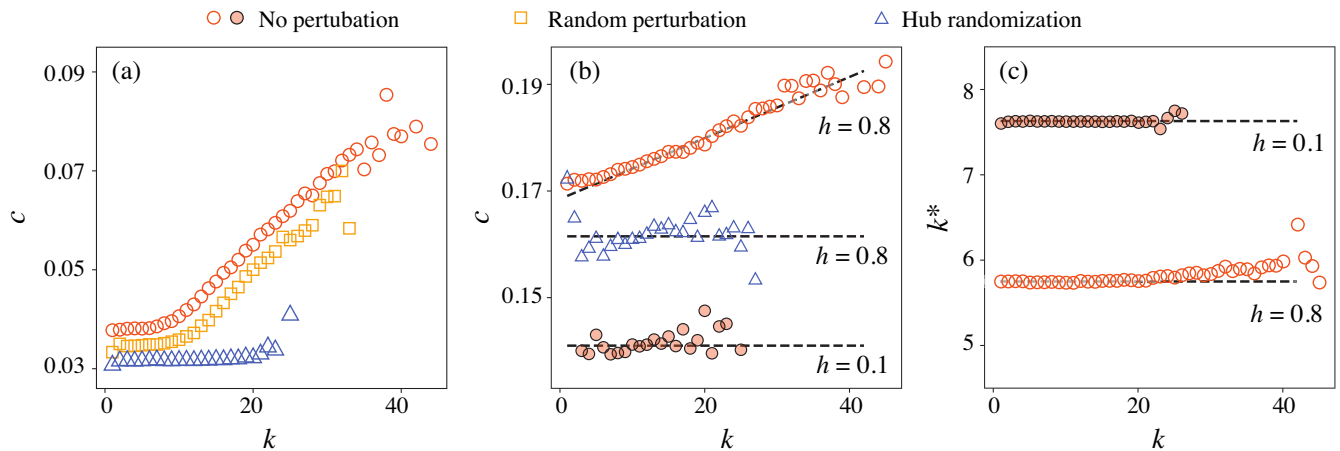


FIG. 4. Hub cells carry most of the cross-correlation content of a β -cell collective. (a) Empirical neighborhood-wide average cross-correlation of nodes c as a function of the node degree k . Open circles, squares, and triangles, respectively, denote no perturbation, random perturbation, and hub randomization. (b) Same as (a), but simulated. Open circles and triangles, respectively, denote no perturbation and random perturbation when coupling, $h = 0.8$ is strong, whereas filled circles denote no perturbation when coupling $h = 0.1$ is weak. (c) The simulated average number of active neighbors k^* as a function of the node degree. Open and solid circles, respectively, denote the strong, $h = 0.8$, and the weak coupling, $h = 0.1$.

Irrespective of the signal origin, empirical or simulated, the properties of functional networks—such as assortativity or the largest eigenvalue of the configuration-ensemble adjacency matrix—all critically depend on the presence of highly connected (i.e., hub) nodes. Our results thus support the hub-cell idea. A similar heterogeneous organization of functional networks has also been discovered in the collectives of chemosensing cells [42,43] communicating via gap junctions.

The support for the hub-cell idea would be a strong blow to electrophysiological theory if nodes in the dynamical network model had any distinctive properties; for example, different degrees or an internal structure. In the model, however, all nodes are completely identical, upholding the ideas of electrophysiological theory that no cell is predisposed for leadership. Leader cells, in fact, emerge through cell-cell communication as evidenced by tracing the degree distributions of functional networks to the coupling strength in the dynamical network model. In the language of the army metaphor, generals do lead, but not by birthright; they get promoted by their peers. Our findings thus not only reconcile the concept of hubs with electrophysiological theory, but also point to an extremely robust architecture of collectives.

Before expanding on the last remark about the robustness of β -cell collectives, we note that a basic property of the network model is the dynamic nature of nodes, whose state fluctuates between active and inactive either intrinsically or depending on time-varying extrinsic influences. Functional networks are constructed from the time series of fluctuating node states by correlating such time series over a time interval that is much longer than the typical transition times of node fluctuations. Therefore, once constructed, functional networks are no longer fluctuating; their properties are static. Moreover, because the degree distribution is an ensemble average over many network realizations, the fluctuations due to sampling are small. The stochastic nature of node states precludes predicting which particular node takes the role of a general, simultaneously allowing that generals rotate on a longer timescale. These particular properties of the model are consistent with physiological considerations because heavy communication activity is energetically taxing for individual cells. β cells in an intact tissue engage in complicated interactions that involve nearest neighbor communication (for instance, through gap junctions) and simultaneous paracrine communication via many signaling molecules. We have shown, however, that by looking solely at the cell-calcium dynamics, the functional role (hub or not) of any given cell emerges as a collective property rather than being bestowed upon specific cells or being determined by spatial positions in the tissue.

Interestingly, there is a physiological advantage provided by the heterogeneity of functional networks. Cells have been shown to use cell-cell distance to optimize their

sensing precision [44]. In compact microorgans such as pancreatic islets, cells cannot easily adjust mutual distances, but could instead use functional-network heterogeneity to sharpen their collective response. Let λ_1 be the largest adjacency-matrix eigenvalue and \mathbf{v}^1 the corresponding eigenvector [32,45]. Because the components of the latter vector quantify the importance of network nodes, we assume that $y_i = \sum_{j \in \Omega_i} v_j^1 x_j = \sum_j a_{ij} v_j^1 x_j$ represents the signal that node i integrates from the nearest neighbors $j \in \Omega_i$, while all other signals are treated as constant-variance noise. Under this assumption, the signal-to-noise ratio of sensing cells is proportional to the variance $\mathbb{E}[y^2] = \sum_{ijk} a_{ij} v_j^1 a_{ik} v_k^1 \text{Cov}(x_j, x_k) \gtrsim c_0 \lambda_1^2$, where c_0 is the cross-correlation threshold used during the construction of functional networks. The sensing precision is thus proportional to λ_1^2 , which would equal $\lambda_1 = 1 + \langle k \rangle$ if functional networks were random, but increases to $\lambda_1 = 1 + \langle k \rangle + \langle k \rangle / r$ because of heterogeneity. Accordingly, cell-cell communication imparts a sharp glucose-sensing acuity to β -cell collectives.

The example on glucose-sensing acuity demonstrates a physiological advantage of heterogeneous functional networks over homogeneous ones. This advantage would, however, come at a cost of vulnerability to hub-node failures [36] if heterogeneity were imprinted in the underlying physical network of β cells. Our results instead strongly favor an interpretation by which influential cells materialize endogenously within β -cell collectives, giving rise to influence hierarchies that are autopoietic, both in the self-producing and self-maintaining sense of this term. All that is needed for hub cells to emerge among identical peers is cell-cell communication, and should a hub fail, there is no obstacle for another one to reemerge as long as communication remains feasible. It would thus seem that in β -cell collectives, biology has managed to create an ultrarobust architecture that is physiologically advantageous as well. This is an impressive feat that could perhaps inspire thinking about the design and engineering of next-generation critical infrastructure.

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