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**Cite this article:** Cervera J, Manzanares JA, Mafe S. 2014 The interplay between cooperativity and diversity in model threshold ensembles. *J. R. Soc. Interface* **11**: 20140099. http://dx.doi.org/10.1098/rsif.2014.0099

Received: 29 January 2014 Accepted: 25 July 2014

#### Subject Areas:

biophysics, nanotechnology

#### **Keywords:**

biological diversity, cooperativity phenomena, threshold response

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Electronic supplementary material is available at http://dx.doi.org/10.1098/rsif.2014.0099 or via http://rsif.royalsocietypublishing.org.



# The interplay between cooperativity and diversity in model threshold ensembles

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The interplay between cooperativity and diversity is crucial for biological ensembles because single molecule experiments show a significant degree of heterogeneity and also for artificial nanostructures because of the high individual variability characteristic of nanoscale units. We study the cross-effects between cooperativity and diversity in model threshold ensembles composed of individually different units that show a cooperative behaviour. The units are modelled as statistical distributions of parameters (the individual threshold potentials here) characterized by central and width distribution values. The simulations show that the interplay between cooperativity and diversity results in ensemble-averaged responses of interest for the understanding of electrical transduction in cell membranes, the experimental characterization of heterogeneous groups of biomolecules and the development of biologically inspired engineering designs with individually different building blocks.

## 1. Introduction

Single-cell dynamic heterogeneity in a population allows fast responses to environmental changes [1,2]. The observed behaviour emerges as a statistical average of the whole cell ensemble that may however show a significant diversity at the single-cell level [2]. The diversity of the basic units in complex biological systems, such as a biomembrane [3,4] and the brain [5,6], increases functionality and reliability. In particular, a certain level of neural response diversity can be beneficial to coding and decoding processes [6,7]. Cooperativity is also a universal characteristic of biological macromolecules, playing a crucial role in enzyme catalysis [8] and ligand binding [9]. The steepness of the stimulus–response to a range of physico-chemical changes in the external environment allows making appropriate decisions in biological systems [9,10]. This is the case of the cells forming the immune system, where the response should be suppressed at low input levels while it should be reinforced when the input exceeds some fixed value [11].

Systems composed of coupled threshold nanostructures may trigger a response over a relatively narrow input region, e.g. a particular potential window for the ion channels in a cell membrane [3,12,13]. A sigmoidal dependence between the system response (conductance, ligand binding, etc.) and the external stimulus (applied potential, ligand concentration, etc.) is typically observed [3,9,10,14–16]. The cooperative response is enhanced when many nominally identical units act in concert, as occurs in a thermodynamic phase transition [14]. However, only a fraction f < 1 of the responsive units should be expected to act cooperatively in a real biological system because of the inherent ensemble heterogeneity revealed by experimental single molecule methods and simulations [9,12,13,16].

The interplay between cooperativity and diversity in a system formed by a finite number of threshold nanostructures constitutes a question of biological relevance because single molecule experiments show a significant heterogeneity in ensembles of biological macromolecules with respect to ligand binding, folding and activity [9]. Remarkably, this question arises also in nanoscience because nanostructures tend to show different individual characteristics [17] and digital switching is central to information processing schemes.

The fundamental physical concepts of biochemical cooperativity and regulation have been discussed in previous monographs [14,15]. A recent study has

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also emphasized the implications of molecular heterogeneity for the cooperative effects observed in ensembles of biological macromolecules [9]. Simulations and single molecule experiments show that this heterogeneity tends to decrease the observed ensemble cooperativity from the intrinsic value characteristic of individual molecules [9]. However, these studies concentrate on chemical binding and folding processes where ligand affinity is the main issue. Alternatively, we study here ensembles of threshold nanostructures making use of a canonical model that incorporates the experimental characteristics observed in the current-applied potential curves of ideal ion channels. Because of the diversity, the units in the ensemble do not show identical individual properties and should then be modelled as a statistical distribution of physical characteristics described by central and width distribution values [9,13,17-20]. This problem is relevant to clusters of pores in biomembranes [3,4,13,16], populations of channels and cell sensing domains [3,21,22] and voltage-gated channels in simple neuronal models [12,18,19,23]. Artificial threshold potential units, such as field-effect nanowires [17,24], carbon nanotubes [25] and single electron transistors based on monolayer protected metallic clusters, show also a high individual variability [17,19].

## 2. Theoretical model

We consider ensembles composed by *N* units with different threshold potentials. The conductances  $G_i = 0$  (closed state) and *G* (open state) of threshold unit *i* occur with probabilities  $1 - P_{o,i}(V)$  and  $P_{o,i}(V)$  dictated by the externally applied potential *V* and the individual threshold potential  $V_{th,i}$  [3,18,26]. The statistical distributions for  $V_{th,i}$  should be obtained from the variability observed in the individual electrical characteristics [5,18,27]. In some biological systems, the diversity can be controlled by mutation and expression [28]. In the case of ion channels, for instance, the different charge distributions along the channels influence the values of  $V_{th,i}$  [3,18,27] and then the channels may show different values of the individual current  $I_i = GVP_{o,i}(V)$  for the same potential *V* (note that  $I_i$  takes high values only for those units in the ensemble having  $V_{th,i} < V$  [3]).

We assume that a fraction (1 - f) of the *N* units does not show cooperativity. For a non-cooperative unit *i* of threshold potential  $V_{\text{th},i}$ , the open-state probability at potential *V* is

$$P_{o,i}(V) = \frac{\exp[zF(V - V_{\text{th},i})/RT]}{1 + \exp[zF(V - V_{\text{th},i})/RT]},$$
(2.1)

where *F* is the Faraday constant, *R* is the gas constant and T = 300 K. As  $(dP_{o,i}/dV)_{V_{th,i}} = zF/4RT$ , the parameter *z* gives the threshold sensitivity in the transition region between the high and low conductance states (in the case of ion channels, *z* is the number of charges involved in gating [3]). In the argument of the exponential in equation (2.1), the electrical energy *zFV* must surpass the effective threshold energy *zFV*<sub>th,i</sub> in order to drive the channel to the open state (the energies are scaled in terms of the thermal energy per mole, *RT*). We have considered the threshold potential *V*<sub>th,i</sub> and the effective gating charge *z* here because these parameters are characteristic of voltage-gated channels, with values in the range *V*<sub>th,i</sub> = 20-80 mV and z = 2-6 [3,12,16,18,20]. Note also that these electrically sensitive channels are basic elements of the biological membranes in both excitable and non-excitable cells.

We will use z = 4 for all *N* units in the ensemble, a typical value for ion channels [3,13]. However, the ensembleaveraged response may exhibit an effective parameter  $z_{eff}$  that can be significantly different from *z*. In particular, diversity should give an extended system response ( $z_{eff} < z$ ) that may be interpreted as an apparent negative cooperativity, as we will show later.

The remaining fN units in the ensemble have the same threshold potential  $V_{\text{th}}^{\circ}$  and form a cooperative cluster. Using a self-consistent, mean-field approach [12,14], their open-state probability is

$$P_{o,c}(V) = \frac{\exp[zF(V - V_{th}^{o})/RT + \alpha P_{o,c}(V)]}{1 + \exp[zF(V - V_{th}^{o})/RT + \alpha P_{o,c}(V)]},$$
 (2.2)

where  $\alpha$  is a dimensionless parameter characterizing the coupling between cooperative units ( $\alpha$  is the molar interaction energy divided by the thermal energy *RT* [12,14]). As  $P_{o,c}(V_{th}^o - RT\alpha/2zF) = 1/2$  and  $(dP_{o,c}/dV)_{P_{o,c}=1/2} = zF/((4 - \alpha)RT)$ , the cooperativity should give a reduction in the effective threshold potential and an increase in the effective value of *z*.

From equations (2.1) and (2.2), the ensemble-averaged open-state probability is

$$\bar{P}_{\rm o}(V) = \frac{1}{N} \sum_{i=1}^{(1-f)N} P_{{\rm o},i}(V) + f P_{{\rm o},c}(V).$$
(2.3)

The probability of equation (2.3) incorporates explicitly the effects of the cooperativity and diversity. These effects are described by the effective values of the threshold potential, determined by the condition  $\bar{P}_{\rm o}(V_{\rm th,eff}) = 1/2$ , and the parameter  $z_{\rm eff} \equiv (4RT/F)(d\bar{P}_{\rm o}/dV)_{\bar{P}_{\rm o}=1/2}$ . Alternatively,  $z_{\rm eff}$  and  $V_{\rm th,eff}$  may be determined by fitting  $\bar{P}_{\rm o}(V)$  in equation (2.3) to the phenomenological equation

$$\bar{P}_{\text{o,eff}}(V) = \frac{\exp[z_{\text{eff}}F(V - V_{\text{th,eff}})/RT]}{1 + \exp[z_{\text{eff}}F(V - V_{\text{th,eff}})/RT]}.$$
(2.4)

This fitting would be the usual experimental procedure if we were to assume a homogeneous ensemble and could be done by minimization of the function  $d(z_{\text{eff}}, V_{\text{th,eff}}) = \sum_{V=0}^{2V_{\text{th}}^{\text{o}}} (\bar{P}_{\text{o,eff}} - \bar{P}_{\text{o}})^2$ , where *V* runs over all the potential values considered.

The simulations are implemented and conducted in standard Python programming language. The code can also be written in Fortran (or another compiled language) to optimize the numerical performance. To assess the goodness of the average probability fitting, we have used the parameter

$$\varepsilon = \sqrt{\frac{\sum_{V} \left[\bar{P}_{o}(V) - \bar{P}_{o,\text{eff}}(V)\right]^{2}}{\sum_{V} \left[\bar{P}_{o}(V)\right]^{2}}},$$
(2.5)

where the sum extends over all the values of potential *V*. The numerator of this parameter indicates the deviation between the average open probability and the effective probability obtained with the fitted values  $z_{\text{eff}}$  and  $V_{\text{th,eff}}$ . The denominator is a normalizing factor. The above parameter gives the relative average error.

The distribution of the threshold potentials  $V_{\text{th},i}$  for the non-cooperative units (i = 1, 2, ..., (1 - f)N) is generated using the algorithm described in appendix A. The above model equations contain the basic characteristics of ensembles composed of systems with different nanostructures acting cooperatively [17,29]. We evaluate  $\bar{P}_{o}(V)$  from equation



**Figure 1.** (*a*) A typical distribution of threshold potentials [13,18,20,27] for N = 100 units with z = 4. The 15 units forming a central cooperative cluster of interaction parameter  $\alpha = 2$  have the common threshold potential  $V_{\rm th}^{\rm o} = 54$  mV, whereas the other (uncoupled) 85 units have values distributed around  $V_{\rm th}^{\rm o}$  with a width  $2V_{\rm th}^{\rm o}\delta$ , where  $\delta = 0.5$  is the diversity parameter. (*b*) Individual open-state probabilities  $P_{\rm o,i}$  (grey curves), ensemble-averaged probabilities  $\bar{P}_{\rm o}$  (bold solid curve) and phenomenological probability  $\bar{P}_{\rm o,eff}(V)$  (dashed curve). The resulting effective values are  $z_{\rm eff} = 2.8$  and  $V_{\rm th,eff} = 53$  mV. Inset: for an ensemble where both the threshold potentials and the parameters *z* of the units followed statistical distributions with  $\delta = 0.5$  and f = 0.15, the effective values would be  $z_{\rm eff} = 2.5$  and  $V_{\rm th,eff} = 52$  mV. (Online version in colour.)

(2.3) and fit the result obtained to the phenomenological equation (2.4) for a large number of statistical distributions (figure 1*a*) obtained with the algorithm in appendix A. The distributions are characterized by prescribed values of the diversity ( $\delta$ ) and cooperativity (f and  $\alpha$ ) parameters. We assume that the threshold units in the tails of the distribution have individual properties so different with respect to the central value characteristic of the cooperative cluster that they cannot be coupled together.

## 3. Results and discussion

Figure 1*b* shows the individual open-state probabilities (grey curves) for the threshold units in the ensemble of figure 1*a* at potential *V*. The effective open-state probability  $\bar{P}_{o,eff}(V)$  (dashed curve) is obtained by fitting equation (2.4) to equation (2.3) for the ensemble-averaged probability  $\bar{P}_{o}$  (bold solid curve). This fitting gives the effective values  $z_{eff} = 2.8$  and  $V_{th,eff} = 53$  mV for an ensemble with diversity parameter  $\delta = 0.5$  and fraction of cooperative units f = 0.15, with z = 4 and the central threshold potential  $V_{th}^{o} = 54$  mV. The units with low threshold potentials respond at low potentials, whereas those having high threshold potentials



**Figure 2.** (*a*) Effective threshold potential and (*b*) effective parameter *z* as a function of the fraction *f* of units acting cooperatively and the diversity parameter  $\delta$ .

do not saturate to  $P_{o,i}(V) = 1$  at high potentials *V* in the range  $V_{\text{th}}^{o} < V < V_{\text{th},i}$ . As expected, the diversity allows a wide response modulation with respect to an individual response (no diversity), which may be an advantage when an extended response over  $V/V_{\text{th}}^{o}$  is desirable [13,19]. However, this diversity effect may be problematic if digital (*on*/ *off*) ensemble-averaged responses are required.

Note that statistical distributions similar to that of figure 1*a* for the threshold potential could also be expected for the parameter *z* of the units. The inset of figure 1*b* shows the individual open-state probabilities obtained with distributions of  $V_{\text{th},i}$  and  $z_{i}$  for  $\delta = 0.5$ . We concentrate, however, on the case z = 4 to better show the interplay between diversity and cooperativity. Extensions to statistical distributions with multiple variables [17] can also be considered at the price of increasing the complexity of the system response.

Figure 2*a*,*b* shows the effects of cooperativity (*f*) and diversity ( $\delta$ ) on the effective values of the threshold potential  $V_{\text{th,eff}}$  and parameter  $z_{\text{eff}}$  for  $\alpha = 2$ . Note that  $V_{\text{th,eff}}$  remains approximately constant with  $\delta$  but it decreases significantly with *f* because the fraction of units acting cooperatively

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**Figure 3.** (*a*)  $z_{\text{eff}}$  and (*b*) error ratio  $(1 - \bar{P}_{0,\alpha=2})/(1 - \bar{P}_{0,\alpha=0})$  as a function of *f* and  $\delta$ . The horizontal dashed line in (*a*) corresponds to the value z = 4 of all units. (*c*)  $(1 - \bar{P}_{0,\alpha})/(1 - \bar{P}_{0,\alpha=0})$  decreases with increasing interaction parameter  $\alpha$  for f = 0.5 and  $\delta = 0.25$  and is insensitive to the number of units *N*. The grey zones correspond to the range of values obtained in the simulations for  $V/V_{\text{th}}^{\text{th}} = 1.5$ . (Online version in colour.)

gives a significant response at potentials close to  $V_{\text{th}}^{\text{o}}$  (figure 1*a*,*b*). Also,  $z_{\text{eff}}$  increases to 6.5 with increasing *f* because of the concerted response of the cooperative units while it decreases to  $z_{\text{eff}} = 3.5$  with increasing  $\delta$  because of the extended response characteristic of diversity. Diversity and cooperative effects can coexist in the ensemble response for intermediate values of  $\delta$  and *f*. For the results of figure 2, parameter  $\varepsilon$  gives a maximum relative error of 4%. The error distribution is Gaussian-like, with a maximum at 1.5% and a width of 0.5% (data not shown).

The above effects are clearly shown in figure 3a for the fixed values  $\delta = 0.25$  (*f* variable) and f = 0.5 ( $\delta$  variable). The grey zones around the bold curves characterize the range of values obtained as a result of the randomness

introduced in the distributions (see also figure 2*b*). The interplay between diversity and cooperativity gives phenomenological, effective ensemble values  $z_{\text{eff}}$  that deviate significantly from the individual value z = 4 of all units. Therefore, the fitting results can be interpreted as effectively positive ( $z_{\text{eff}} > 4$ ) or effectively negative ( $z_{\text{eff}} < 4$ ) cooperativity [9].

Figure 3*b* shows the ratio  $(1 - \bar{P}_{o,\alpha=2})/(1 - \bar{P}_{o,\alpha=0})$  as a function of  $f(\delta = 0.25)$  and as a function of  $\delta(f = 0.5)$ , where  $1 - \bar{P}_o$  is the ensemble-averaged probability of the closed state. This probability constitutes then a measure of the error obtained when trying to drive the ensemble from the closed to the open (conductive) state at a given potential *V*. Note that  $1 - \bar{P}_{o,\alpha=2} < 1 - \bar{P}_{o,\alpha=0}$  because of the enhanced response characteristic of the ensemble coupling at  $\alpha = 2$ . The ratio  $(1 - \bar{P}_{o,\alpha=2})/(1 - \bar{P}_{o,\alpha=0})$  can then be regarded as the relative change obtained in the ensemble switching error because of the effects of the diversity  $\delta$  and the cooperativity *f*. The diversity may increase the error ratio to values close to unity, making almost negligible the constructive role of cooperativity in decreasing the switching error.

The negative effect of diversity for digital switching at fixed cooperative fraction *f* can be counteracted by increasing the coupling parameter  $\alpha$ . Figure 3*c* shows that the error ratio  $(1 - \bar{P}_{o,\alpha})/(1 - \bar{P}_{o,\alpha=0})$  decreases with increasing  $\alpha$  at constant *f* and  $\delta$  (note that the range of  $\alpha$  values considered does not include the critical value  $\alpha = 4$  [29]) while it remains approximately constant with the number of units *N*. However, the fluctuations of the ratio  $(1 - \bar{P}_{o,\alpha})/(1 - \bar{P}_{o,\alpha=0})$  with respect to the average value tend to decrease significantly with *N*.

We have considered so far the ensemble response to static potentials *V*. The ensemble response to a time-dependent potential V(t) is characterized by the correlation coefficient *C* between the *input* signal V(t) and the *output* average current per unit,  $\overline{I}(t)$ , as

$$C = \frac{\langle V\bar{I} \rangle - \langle V \rangle \langle \bar{I} \rangle}{\sqrt{\langle V^2 \rangle - \langle V \rangle^2} \sqrt{\langle \bar{I}^2 \rangle - \langle \bar{I} \rangle^2}},$$
(3.1)

where the angle brackets denote time averages over the period  $\tau$  of the external potential

$$V(t) = V_0 + V_1 \cos(2\pi t/\tau). \tag{3.2}$$

The signal V(t) of offset potential  $V_0$  and amplitude  $V_1$  is applied to all individual units in a parallel ensemble, assuming no time delay in the ensemble response. To this end, the period  $\tau$  should be much longer than the characteristic response time of the system (the adiabatic limit). This condition is approximately valid for nanostructures such as ion channels [30] and nanopores [31] because of the small solution volumes involved.

Figure 4*a* shows the unit average current characterizing the response to the time-dependent sub-threshold potential of equation (3.2). The grey zones around the bold curves correspond to the range of values obtained for the different distributions of threshold potentials (figure 1*a*). Figure 4*b* shows the correlation *C* between the *input V*(*t*) and the *output*  $\overline{I}(t)$  signals for different values of *f* and  $\delta$ . The combination of a high cooperativity with a low diversity gives a high *output* (current) at the price of a low *output/input* correlation. When *f* is close to zero, the diversity allows for a better reconstruction of the weak input signal. This significant increase of the correlation with increasing ensemble diversity

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**Figure 4.** (*a*) The potential *V*(*t*) of equation (3.2) for  $V_0 = V_1 = 0.5 V_{th}^{o}$  (left, dashed curve) and the average current per unit in dimensionless form,  $\bar{I}(t)/I_0 = \bar{P}_0 V(t)/V_{th}^{o}$  (right, solid curves), where  $I_0 = G V_{th}^{o}$ . The values for *f* and  $\delta$  in the curves correspond to the limiting cases of high cooperativity (*f* = 0.95 and  $\delta$  = 0.05) and high diversity (*f* = 0.05 and  $\delta$  = 0.50) considered here. (*b*) Correlation *C* between the *input* potential and the *output* current as a function of *f* and  $\delta$ .

occurs because low threshold units detect the low values of the *input* signal while high threshold units avoid saturation at the high values of the signal [19].

It is in order now to discuss the biological relevance of the physical results obtained. In particular, these results show some of the essential physical trends that are characteristic of the following.

(i) Mechano-sensitive channels forming self-organized clusters over the cell surface membrane. In this case, the collective response is based on cooperative gating of the elastic interactions in spatially organized membrane proteins [32,33]. Note in this context the close analogy between mechanically and electrically sensitive channels. Indeed, fig. 2 of [34] shows that similar gating effects are obtained in mechanically and electrically sensitive ion channels if we substitute elastic forces for electrical forces. The diversity and coupling effects described here can then be relevant to mechano-electrical transduction because these effects can modulate the collective response in the presence of large stimuli, avoiding saturation and allowing operating ranges with different sensing degrees (see figures 2b, 3a and 4a here). Moderate threshold diversity may also allow for the extended dynamic range [13,19] required for monitoring a continuously changing ambient, while cooperativity should provide a more robust response for a prescribed stimuli region.

- (ii) For the case of electrically sensitive channels, patches of leaky domains (low threshold potential channels) may coexist with other low conductive domains (high threshold potential channels) thus allowing a heterogeneous transmission of electrical signals across the membrane that may be relevant to cell growth and differentiation [12,13,22].
- (iii) Biochemical systems characterized by a significant molecular heterogeneity, as revealed by single molecule experimental methods [9]. We have shown how diversity can produce ensemble-averaged cooperative effects that differ significantly from those expected for identical threshold potential units (figures 2a,b and 3a), in qualitative agreement with recent experiments and simulations of ligand binding to macromolecules [9]. Note that equation (2.1) and figure 1b are formally analogous to the Hill equation for describing ligand binding (see eqn (1) and fig. 1b of [9]) if we change the potential-dependent Boltzmann factor to the ligand concentration [9,14,15]. Indeed, the results in figure 3a for the threshold sensitivity in the transition region between the high and low conductance states here can be compared qualitatively with those of fig. 1c of [9] for the cooperative parameter describing binding cooperativity in a heterogeneous population of molecules.
- (iv) Fluctuations in biological nanoscale systems due to diversity effects. We have shown here that the tails in the statistical distributions of the properties characteristic of molecular populations (figure 1*a*) provide a natural flexibility that can be exploited in biological features. In noisy gene expression, for example, genetic circuits acting as switches must make a trial between two different outcomes (e.g. pathogens making probabilistic choices between latency or activity; see fig. 2 of [35]) and the tails of the statistical distributions are crucial in the system response to environmental fluctuations [35].
- Digital switching schemes based on cooperative nanos-(v) tructures showing different individual characteristics [17,29]. The diversity observed in natural systems composed of many interacting units allows for modulating the collective response to weak external signals [1,2,11]. This fact suggests bioengineering schemes based on populations with distributed thresholds similar to those of figure 1a. The variability in the individual responses should permit the processing of a wide range of input signals, avoiding saturation (figure 4a and Cervera et al. [17]). In turn, the cooperativity may decrease the switching errors produced when trying to drive the system from the closed to the open state at potential V (figure 3b,c), yielding an approximately defined digital response [29].

## 4. Conclusion

The interplay between cooperativity and diversity is at the interface between biology and nanoscale engineering. A complex system formed by many basic units coupled together can work reliably over an extended range of inputs despite the high individual variability of the units. For instance, biological cell ensembles may show a high heterogeneity but the individual differences are usually normalized in a functional tissue [36]. How could this regulation leading to a correct average behaviour be achieved? This question has also significant implications for nanoscience and biologically inspired designs [17,19,24,25,29,37,38] because of the variability characteristic of individual nanostructures coupled in close packed configurations.

We have addressed here the problem of threshold ensembles processing both static and time-dependent electrical signals. The simulations show that the interplay between cooperativity and diversity ultimately results in ensembleaveraged responses characterized by an extended dynamic range, but still showing approximately defined *on* and *off* states. The model results should be of interest for ion channels performing mechanical and electrical transduction in cell membranes, biochemical ensembles of molecules characterized by a significant heterogeneity and biologically inspired schemes for information processing based on nanoscale building blocks.

Funding statement. We acknowledge the financial support from the Ministry of Economic Affairs and Competitiveness and FEDER (project MAT2012-32084) and the Generalitat Valenciana (project PROMETEO/GV/0069, Programme of Excellence).

## Appendix A

The distribution of threshold potentials  $V_{\text{th},i}$  of the noncooperative units (i = 1, 2, ..., (1-f)N) (figure 1*a*) is generated using the following algorithm. The values are

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- distributed in the range  $(1-\delta)V_{\text{th}}^{o} \leq V_{\text{th},i} \leq (1+\delta)V_{\text{th}}^{o}$ , where  $V_{\text{th}}^{o}$  is the central value and  $\delta$  is the relative width. The above range is divided into (2J+1) intervals of identical width  $\Delta V = 2\delta V_{\text{th}}^{o}/(2J+1)$ , which are numbered as  $j = -J, -J + 1, \ldots, 0, \ldots, J - 1, J$ . The threshold potential values  $V_{\text{th},i}$  within interval j are generated randomly and hence are slightly different. The fraction of threshold potentials that lie within interval j is also generated randomly but it follows approximately a Gaussian probability distribution. The probability that  $V_{\text{th},i}$  is in any interval j in the range  $-k \leq j \leq k$  is  $P_k = \sum_{j=0}^{k} p_j$ , where  $p_j = (1/\Sigma) \exp[-2\delta j^2/((2J+1)^2(1-f))]$  is the probability that  $V_{\text{th},i}$  lies in the intervals -j or +j and  $\Sigma$  is determined by the normalization condition,  $P_J = \sum_{j=0}^{J} p_j = 1$ .
- To ensure that  $\delta$  is the relative width of the distribution, one threshold potential is located at one end of the range by generating a random number  $r_1$  and assigning  $V_{\text{th},1} = (1 - \delta)V_{\text{th}}^{\circ}$  if  $r_1 < 0.5$  or  $V_{\text{th},1} = (1 + \delta)V_{\text{th}}^{\circ}$  if  $r_1 > 0.5$ . The generation of the remaining threshold potentials requires three random numbers between 0 and 1,  $r_i$ ,  $s_i$  and  $t_i$ , for each  $V_{\text{th},i}$ . The number  $r_i$ determines the interval j where  $V_{\text{th},i}$  lies. As  $0 < P_k \le 1$  for any k ( $0 \le k \le J$ ),  $r_i$  can be compared to the cumulative probabilities { $P_0, P_1, \ldots, P_J = 1$ }, which satisfy  $P_k < P_{k+1}$  for  $0 \le$ k < J. If  $P_j$  is the smallest probability that is larger than  $r_i$ , then  $V_{\text{th},i}$  lies in the intervals -j or +j and its random value is  $V_{\text{th},i} = V_{\text{th}}^{\circ} + (0.5 - s_i + j \operatorname{sgn}(t_i - 0.5))\Delta V$ . Actually, only low ( $s_i < 0.45$ ) or high ( $s_i > 0.55$ ) values of  $s_i$  are accepted to avoid non-cooperative units with threshold potentials too close to  $V_{\text{th}}^{\circ}$ .

A Python program that implements this algorithm is provided as electronic supplementary material.

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