SNT-2 appears to tightly co-localize with NLP-40 in the intestine, and mutation of the SNT-2 calcium binding domains phenocopies both the *snt-2* null allele and the RNAi knockdown. These results imply that NLP-40 is released from DCVs in response to calcium peaks from the intestine.

The authors also identified a putative NLP-40 receptor, the GPCR homologue AEX-2. The *aex-2* mutants, like the *nlp-40* mutants, lack the Exp (as well as the aBoc) step [11]. In addition, *aex-2* reporters are expressed in the DVB motor neuron, the presumed target of NLP-40 *in vivo*. The authors further demonstrated that synthetic NLP-40 peptides could activate heterologously-expressed AEX-2 in an *in vitro* assay system. Thus, AEX-2 appears to be an authentic receptor for NLP-40 peptides.

Finally, the authors addressed the question of how NLP-40 activates the DVB neurons: does it potentiate the response to a primary neurotransmitter, or are NLP-40 peptides themselves primary neurotransmitters? Consistent with the latter hypothesis, they observed that mutants defective in the biosynthesis, transport or release of each of the classical neurotransmitters (acetylcholine, glutamate, and monoamines) all failed to display any dysfunction in the Exp step. Furthermore, microinjection of synthetic NLP-40 peptides into the pseudocoelomic space between the intestine and the body wall muscles acutely triggered DVB excitation. Taken together, these results suggest that NLP-40 peptides indeed act like classical neurotransmitters to acutely depolarize the DVB motorneurons.

The role for neuropeptide signaling in the *C. elegans* defecation circuit is perhaps not as unusual as it might seem at first glance. While neuropeptides are typically thought of as cotransmitters that modify the actions of fast-acting classical neurotransmitters, their ability to independently modulate neuronal excitability has parallels in, for example, the fly olfactory system [13]. Indeed, neuropeptide-gated cation channels have been identified in molluscs and *Hydra* [14,15], though homologous molecules have not been identified in other organisms. Additionally, the release of neuromodulatory peptides such as ghrelin from gut cells is also a well-established phenomenon [16]. Finally, other neuropeptides have been shown to be important for biological timing; the role of PDF in modulating the circadian clock is a notable example [17].

Nonetheless, the regulated release of an intestinal peptide to trigger individually timed neuronal depolarizations on a time scale of a few seconds still seems a rather unexpected way to coordinate a motor program. Whether such a mechanism represents a unique solution to the challenges of a nervous system with an extremely low cell number, or whether similar processes occur in bigger nervous systems, is anyone's guess. But clearly there is much to learn about how neuropeptides can contribute to the functions of neural circuits.

References

1. Doi, M., and Iwasaki, K. (2002). Regulation of retrograde signaling at neuromuscular junctions by the novel C2 domain protein AEX-1. Neuron *33*, 249–259.
2. Branicky, R., Shibata, Y., Feng, J., and Hekimi, S. (2001). Phenotypic and suppressor analysis of defecation in *clk-1* mutants reveals that reaction to changes in temperature is an active process in *Caenorhabditis elegans*. Genetics *159*, 997–1006.
3. Feng, J., Bussière, F., and Hekimi, S. (2001). Mitochondrial electron transport is a key determinant of life span in *Caenorhabditis elegans*. Dev. Cell *1*, 633–644.
4. Thomas, J.H. (1990). Genetic analysis of defecation in *Caenorhabditis elegans*. Genetics *124*, 855–872.
5. Dal Santo, P., Logan, M.A., Chisholm, A.D., and Jorgensen, E.M. (1999). The inositol trisphosphate receptor regulates a 50-second behavioral rhythm in *C. elegans*. Cell *98*, 757–767.
6. Beg, A.A., Ernstrom, G.G., Nix, P., Davis, M.W., and Jorgensen, E.M. (2008). Protons act as a transmitter for muscle contraction in *C. elegans*. Cell *132*, 149–160.
7. Pfeiffer, J., Johnson, D., and Nehrke, K. (2008). Oscillatory transepithelial H+ flux regulates a rhythmic behavior in *C. elegans*. Curr. Biol. *18*, 297–302.
8. McIntire, S.L., Jorgensen, E., Kaplan, J., and Horvitz, H.R. (1993). The GABAergic nervous system of *Caenorhabditis elegans*. Nature *364*, 337–341.
9. Beg, A.A., and Jorgensen, E.M. (2003). EXP-1 is an excitatory GABA-gated cation channel. Nat. Neurosci. *6*, 1145–1152.
10. Husson, S.J., Clynen, E., Baggerman, G., Janssen, T., and Schoofs, L. (2006). Defective processing of neuropeptide precursors in *Caenorhabditis elegans* lacking proprotein convertase 2 (KPC-2/EGL-3): mutant analysis by mass spectrometry. J. Neurochem. *98*, 1999–2012.
11. Mahoney, T.R., Luo, S., Round, E.K., Brauner, M., Gottschalk, A., Thomas, J.H., and Nonet, M.L. (2008). Intestinal signaling to GABAergic neurons regulates a rhythmic behavior in *Caenorhabditis elegans*. Proc. Natl. Acad. Sci. USA *105*, 16350–16355.
12. Wang, H., Girskis, K., Janssen, T., Chan, J.P., Dasgupta, K., Knowles, J.A., Schoofs, L., and Sieburth, D. (2013). Neuropeptide secreted from a pacemaker activates neurons to control a rhythmic behavior. Curr. Biol. *23*, 746–754.
13. Ignell, R., Root, C.M., Birse, R.T., Wang, J.W., Nässel, D.R., and Winther, A.M.E. (2009). Presynaptic peptidergic modulation of olfactory receptor neurons in *Drosophila*. Proc. Natl. Acad. Sci. USA *106*, 13070–13075.
14. Lingueglia, E., Champigny, G., Lazdunski, M., and Barbry, P. (1995). Cloning of the amiloride-sensitive FMRFamide peptide-gated sodium channel. Nature *378*, 730–733.
15. Golubovic, A., Kuhn, A., Williamson, M., Kalbacher, H., Holstein, T.W., Grimmelikhuijzen, C.J.P., and Gründer, S. (2007). A peptide-gated ion channel from the freshwater polyp *Hydra*. J. Biol. Chem. *282*, 35098–35103.
16. Diano, S., Farr, S.A., Benoit, S.C., McNay, E.C., da Silva, I., Horvath, B., Gaskin, F.S., Nonaka, N., Jaeger, L.B., Banks, W.A., *et al*. (2006). Ghrelin controls hippocampal spine synapse density and memory performance. Nat. Neurosci. *9*, 381–388.
17. Park, J.H., Helfrich-Förster, C., Lee, G., Liu, L., Rosbash, M., and Hall, J.C. (2000). Differential regulation of circadian pacemaker output by separate clock genes in *Drosophila*. Proc. Natl. Acad. Sci. USA *97*, 3608–3613.

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Visual Perception: One World from Two Eyes

Binocular vision requires us to match up the different views of the world seen by each eye. Computational models of primary visual cortex describe how the brain begins this process. Recurrent connections help suppress the response to false matches.

Jenny Read[1] and Fredrik Allenmark[2]

Because our eyes are offset from one another, objects in the world generally project to different retinal locations in the two eyes. Stereo '3D' vision is the ability to deduce information about object distance from these binocular

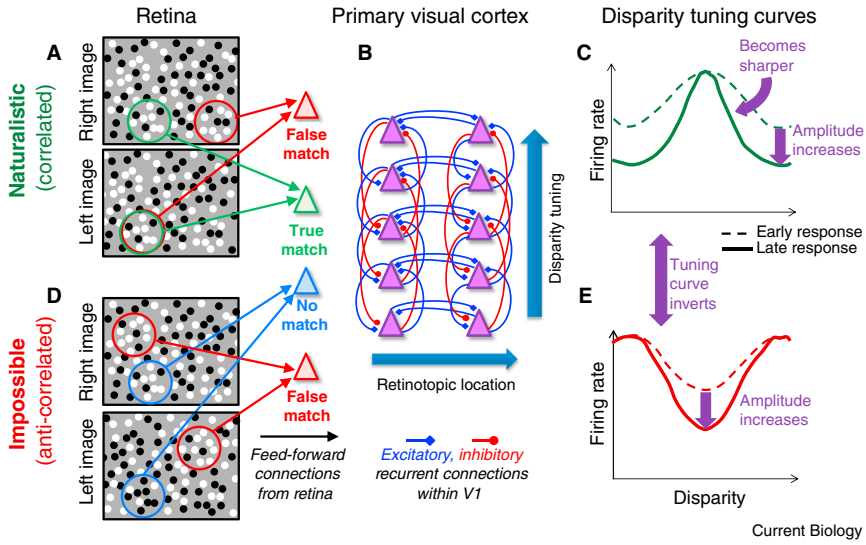

Figure 1. Solving the correspondence problem of stereo vision.

(A) Random-dot stereo-pair. The right eye's image is shifted slightly compared to the left; this is the image's *binocular disparity*. To compute this disparity, the brain must solve the *correspondence problem* — that is, identify image-patches which are identical in the two eyes. The problem is that V1 neurons (triangles) are insensitive to the precise pattern of light within their receptive fields (RFs, circles). The green neuron is tuned to the true disparity, but the red neuron responds just as strongly, because it is seeing a *false match* which happens to contain the same number of black and white dots in each receptive field. (B) Recurrent connections within V1. Blue lines show reciprocal excitation between cells at different retinotopic locations with the same disparity tuning, and between cells at the same location with similar disparity tuning. Red lines show reciprocal inhibition between cells with dissimilar disparity tuning. (C) Normalised disparity tuning curve — that is, the average response of a model neuron to many different images like those in A, with varying disparity. Thin dashed line shows tuning in the first few iterations after stimulus onset; thick line, later in the simulation. The tuning becomes sharper over time. (D) Impossible (anti-correlated) stereopair. At the stimulus disparity, image-patches in each eye are now photographic negatives of one another (blue circles). (E) Tuning curve for anti-correlated stimuli. The tuning curve amplifies over time, but does not become sharper. (C,E adapted from [1].)

disparities in image position. However, this requires the brain to figure out which features in the two retinas were produced by the same object in the world. This matching-up process is known as *stereo correspondence*. It begins in primary visual cortex (V1), the first place in the visual pathway where single neurons receive information from both eyes.

Many V1 neurons are tuned to binocular disparity (Figure 1A). Over the past two decades, increasingly sophisticated computational models of V1 neurons have been produced, but the models still fail to capture all the properties of the V1 neurons, notably how disparity tuning sharpens over time. Now, Samonds *et al.* [1] have shown that a model in which V1 cells mutually influence each other via recurrent connections can quantitatively account for the dynamics of real neurons.

A breakthrough in our understanding of disparity-tuned V1 neurons came with the introduction of the stereo-energy model [2]. This postulates linear receptive fields in each eye, which compute a weighted sum of the retinal image. The left-eye and right-eye sums are added, then the total is squared. The energy model successfully captures many aspects of disparity tuning, including the diverse types of tuning found in V1. Real V1 neurons vary in their tuning to 'position disparity' and 'phase disparity' [3]. A cell's preferred phase disparity describes the shape of its disparity tuning curve (see examples in Figure 2A), whereas its preferred position disparity determines the location of the curve along the disparity axis. Natural images have zero phase disparity, but in the lab it is possible to create stereo pairs with arbitrary phase disparity. A phase disparity of π produces 'anti-correlated' images, in which one eye's image is the photographic negative of the other (Figure 1D). Impressively, the energy model correctly predicts the inverted disparity tuning obtained with these impossible images [4].

In the two decades since the stereo-energy model was introduced, however, a number of discrepancies have been found between its predictions and the behaviour of real neurons. Notably, real neurons show weaker disparity tuning to anti-correlated stereograms, whereas the stereo-energy model responds as strongly for correlated [4]. The precise shape of disparity tuning curves is not related to cells' temporal and spatial frequency tuning as predicted by the energy model [5,6]. Furthermore, real cells become more sharply tuned to disparity over time [7,8] (Figure 1C,E); again, these dynamics cannot be explained by the stereo-energy model.

Computational neuroscientists have considered various tweaks to improve the energy model. Some problems can be solved simply by adding additional output nonlinearities [9,10], or by passing inputs from left and right eyes through a threshold before summing them [11,12]. In particular, several modellers have proposed that disparity-tuned cells receive inhibitory inputs from cells with different disparity tuning [5,8,9,13,14].

All these models have, so far, been feed-forward. That is, one set of cells is used as 'building-blocks' to construct more complex cells in a subsequent layer or cortical area [9,14]. Samonds *et al.* [1] have now taken these ideas to the next stage by modelling an entire population of disparity-tuned cells, over 112,000 in total, all wired together in a network of recurrent connections (Figure 1B). They show that this recurrent model can account *both* for the reduced response to anti-correlated stereograms, and *also* for the temporal dynamics.

How does the model achieve these results? Disparity tuning in naturalistic images requires a non-linearity after inputs from the two eyes are combined. In the original energy model [2], this was achieved by a squaring operation. In the new model [1], the squaring is strengthened by a second nonlinearity relating membrane potential to firing rate. These expansive nonlinearities help reduce the response to impossible stimuli in 'TE'-type cells, which respond strongly to one preferred disparity. They can also help sharpen responses if the mean firing rate is increasing over time. However,

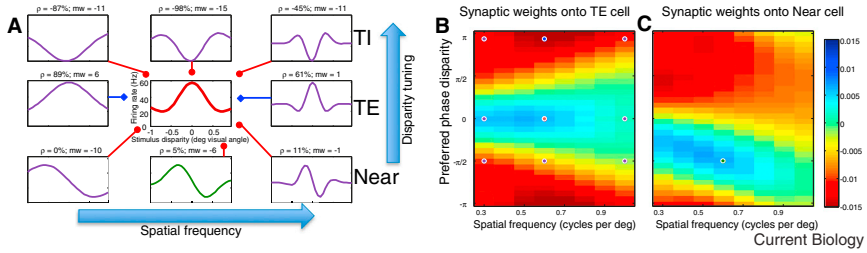

Figure 2. Synaptic weights in the recurrent model of Samonds *et al*. [1].

(A) Feedforward disparity tuning curves (without recurrent connections). The central panel shows one example cell (spatial frequency 0.6 cpd, phase disparity = 0; a tuned-excitatory 'TE' type cell [19]; red dot in B). Surrounding panels show feedforward disparity tuning for eight other cells at the same retinotopic location. Arrows show synaptic connections between these cells and the central cell (red disks, inhibitory; blue diamonds, excitatory). (B) Synaptic weights onto central TE cell from all 256 cells at this retinal location. They vary in phase disparity and spatial frequency. (C) Synaptic weights onto a Near cell (phase disparity $-\pi/2$; green curve in A). These weights, w, are related to the cross-correlation, ρ, between the feedforward tuning curves, shown above each curve for comparison; w is not simply related to ρ, as tuning curves were thresholded at their median before being cross-correlated. A constant was then subtracted for network stability, making 75% of weights inhibitory. And finally, the 256 synaptic weights onto each neuron were normalised such that they summed to –1.2 (these details, tuning curves and weight matrix supplied by Brian Potetz and Jason Samonds, personal communication).

Samonds *et al.* [1] report that their recurrent connections can sharpen disparity tuning over time, even when the mean firing rate is flat or falling. The recurrent connections are also essential for reducing the response to impossible stimuli in 'TI'-type cells, which are strongly inhibited by one particular disparity.

To understand how this happens, we have to take a closer look at the synaptic weights. Cells with different retinotopic locations, but with identical disparity tuning, excite one another, and do so more strongly the closer they are (horizontal recurrent connections in Figure 1B). This recalls the earliest 'cooperative' algorithms proposed to solve the correspondence problem by Julesz, Marr and Poggio [15,16]. Real visual scenes tend to vary fairly smoothly in depth, because they are largely made up of continuous objects and surfaces, with large jumps in disparity only at object boundaries. Thus, correct matches are usually flanked by other matches of similar disparity, whereas false matches occur in isolation. Many stereo algorithms therefore include some form of 'smoothness constraint', such as mutual excitation between nearby disparity sensors tuned to the same depth.

For cells at the same retinotopic location, the synaptic weights depend on the similarity between their disparity tuning (vertical connections in Figure 1B). Figure 2A shows the disparity tuning curve for one sample TE-type cell (red) and eight neighbouring cells at the same retinotopic location (blue). These differ either in the type (TI, Near) or spatial scale of their disparity tuning. The arrows show synaptic weights from the eight neighbouring cells onto the central cell. The central cell is inhibited by cells tuned to different disparities, and most strongly by its TI-type neighbour, which has opposite disparity tuning. This is consistent with a recent theory that cells tuned to impossible phase disparities may suppress TE-type cells, which are tuned to the natural phase disparity of zero, and is supported by recent physiology [8,13].

In contrast, the cell receives excitatory input from its neighbours tuned to similar disparities but at different spatial scales (blue diamonds in Figure 2A). Interestingly, this excitation across spatial scales is asymmetric: excitation is stronger from low-frequency cells onto high-frequency cells than vice versa (Figure 2B,C). Thus, the model incorporates a form of coarse-to-fine encoding. This idea has a long history in theories of stereo vision [17] and is also supported by recent physiology [8,18].

Together, these three properties enable the population to gradually strengthen and sharpen its response to true matches while suppressing the response to false matches. As Figure 1A shows, individual cells initially respond both to true and false matches. However, a true match will activate neurons across many different spatial scales. These mutually reinforce one another via excitatory recurrent connections (blue diamonds in Figure 2A). Because the disparity is uniform across the stimulus, nearby cells tuned to the same disparity will also see mutually-reinforcing true matches. The lateral connections will tend to strengthen the response still further, via the smoothness constraint. Because false matches are due to random clusters of image features which happen to excite one particular neuron, they will not extend across spatial scales or retinotopic locations, and so the neurons responding to false matches will not be boosted in this way.

In impossible stimuli, by definition, there *are* no true matches. Individual energy-model cells will respond to random false matches (circled in red in Figure 1D). However, as before, the response to a false match is not boosted, and indeed is often dampened by cells responding to other false matches. Thus, impossible stimuli produce weaker disparity tuning which does not sharpen over time as with naturalistic stimuli.

Samonds *et al.* [1] have skilfully combined many ideas within the stereo vision literature to produce the most complete model of V1 disparity tuning to date. Their model successfully accounts for many challenging features of neuronal behaviour. It will doubtless be widely used by physiologists and computational neuroscientists. This is a step forward not only for our understanding of disparity encoding in primary visual cortex, but for our understanding of human 3D depth perception.

References

1. Samonds, J.M., Potetz, B.R., Tyler, C.W., and Lee, T.S. (2013). Recurrent connectivity can account for the dynamics of disparity processing in v1. J. Neurosci. *33*, 2934–2946.
2. Ohzawa, I., DeAngelis, G.C., and Freeman, R.D. (1990). Stereoscopic depth discrimination in the visual cortex: neurons ideally suited as disparity detectors. Science *249*, 1037–1041.
3. Cumming, B.G., and DeAngelis, G.C. (2001). The physiology of stereopsis. Annu. Rev. Neurosci. *24*, 203–238.
4. Cumming, B.G., and Parker, A.J. (1997). Responses of primary visual cortical neurons to binocular disparity without depth perception. Nature *389*, 280–283.
5. Read, J.C.A., and Cumming, B.G. (2003). Testing quantitative models of binocular disparity selectivity in primary visual cortex. J. Neurophysiol. *90*, 2795–2817.

6. Read, J.C.A., and Cumming, B.G. (2005). The effect of interocular delay on disparity selective V1 neurons: relationship to stereoacuity and the Pulfrich effect. J. Neurophysiol. *94*, 1541–1553.
7. Menz, M.D., and Freeman, R.D. (2004). Temporal dynamics of binocular disparity processing in the central visual pathway. J. Neurophysiol. *91*, 1782–1793.
8. Tanabe, S., Haefner, R.M., and Cumming, B.G. (2011). Suppressive mechanisms in monkey V1 help to solve the stereo correspondence problem. J. Neurosci. *31*, 8295–8305.
9. Haefner, R.M., and Cumming, B.G. (2008). Adaptation to natural binocular disparities in primate V1 explained by a generalized energy model. Neuron *57*, 147–158.
10. Lippert, J., and Wagner, H. (2001). A threshold explains modulation of neural responses to opposite-contrast stereograms. Neuroreport *12*, 3205–3208.
11. Read, J.C.A., Parker, A.J., and Cumming, B.G. (2002). A simple model accounts for the reduced response of disparity-tuned V1 neurons to anti-correlated images. Vis. Neurosci. *19*, 735–753.
12. Tanaka, H., and Ohzawa, I. (2006). Neural basis for stereopsis from second-order contrast cues. J. Neurosci. *26*, 4370–4382.
13. Read, J.C.A., and Cumming, B.G. (2007). Sensors for impossible stimuli may solve the stereo correspondence problem. Nat. Neurosci. *10*, 1322–1328.
14. Tanabe, S., and Cumming, B.G. (2008). Mechanisms underlying the transformation of disparity signals from V1 to V2 in the macaque. J. Neurosci. *28*, 11304–11314.
15. Marr, D., and Poggio, T. (1976). Cooperative computation of stereo disparity. Science *194*, 283–287.
16. Julesz, B. (1971). Foundations of Cyclopean Perception (Chicago: University of Chicago Press).
17. Marr, D., and Poggio, T. (1979). A computational theory of human stereo vision. Proc. R. Soc. Lond. B *204*, 301–328.
18. Menz, M.D., and Freeman, R.D. (2003). Stereoscopic depth processing in the visual cortex: a coarse-to-fine mechanism. Nat. Neurosci. *6*, 59–65.
19. DeAngelis, G.C., Ohzawa, I., and Freeman, R.D. (1991). Depth is encoded in the visual cortex by a specialised receptive field structure. Nature *352*, 156–159.

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Social Evolution: Reciprocity There Is

The theory of cooperation predicts that altruism can be established by reciprocity, yet empirical evidence from nature is contentious. Increasingly though, experimental results from social vertebrates challenge the nearly exclusive explanatory power of relatedness for the evolution of cooperation.

Michael Taborsky

The theory of social evolution made big leaps in the sixties and seventies of the last century when behavioural biologists started to apply rigorous Darwinian thinking to the problems of competition and cooperation among conspecifics. William D. Hamilton detected and formalized the crucial importance of relatedness for the evolution of cooperation [1], John Maynard Smith developed evolutionary game theory as a tool to understand competitive interactions [2], and Robert Trivers figured out how cooperation might evolve also between unrelated social partners by reciprocal altruism, if received help enhances the recipient's cooperativeness [3]. Some forty years and hundreds of studies later, there is consensus among theoreticians and empiricists that assortment by relatedness is of paramount importance for the evolution of cooperative and competitive behaviour. There is general conviction also that animals cooperating or competing for resources use decision rules optimized by natural selection that can be adequately modelled with the help of evolutionary game theory. In contrast, there is less agreement about the importance of reciprocity for understanding interactions among social partners. It has been questioned whether situations in nature are favourable for reciprocal altruism to evolve [4]. Nevertheless, new evidence from vampire bats shows that reciprocal exchange can indeed be more important for cooperation than relatedness [5].

It is easy to understand the grave doubts about the evolution of cooperation by reciprocity. Helping is costly to donors and beneficial to recipients, which reflects the essential meaning of altruistic behaviour; therefore, selection favours free-riders accepting help without return [3]. However, reciprocity can generate evolutionarily stable cooperation if costly help sufficiently increases the likelihood that donors obtain fitness benefits in return for helping, provided that the benefits more than compensate for the costs of initial investment. This means that the benefit from being helped must on average exceed the cost of helping, and that social interactions should be sufficiently frequent. At the proximate, mechanistic level, reciprocity involves considering information about the likelihood of getting adequate returns of any help provided to a social partner. Such information can be obtained from experience of previous interactions and can generate one of three decision rules: first, in the simplest case, an individual will become more helpful if it received help. This rule — 'help anyone if helped by someone' — can generate evolutionarily stable levels of cooperation in a population [6,7], and such 'generalized reciprocity' is known to operate in rats and humans [8,9]. Second, if social partners interact repeatedly with each other, having received previous help from your social partner can make the recipient more helpful. This rule — 'help someone who has helped you before' — can again spawn stable cooperation [10], and experiments showed that such 'direct reciprocity' can be applied at least by mammals and birds [11–13]. Third, individuals might help a social partner depending on its helpfulness towards others, even if they themselves never received any help. Such 'indirect reciprocity' based on the reputation of social partners can create stable cooperation if individuals are capable of using the respective information [14], but the underlying decision rule 'help someone who is helpful' has been experimentally demonstrated only in humans [15].

To test which (if any) of these reciprocity mechanisms animals employ requires careful experimentation. Whether such mechanisms apply also in nature is an altogether different question. Cooperation among animals in the wild becomes particularly interesting if shown among unrelated individuals, because then its evolution cannot be explained by kin selection [1]. One prominent textbook example is the donation of blood among conspecifics in vampire bats (Figure 1). As Gerald Wilkinson had observed in a natural