

intramolecular DID–DAD interaction. Yet, the actual identity and stoichiometry of the interaction remains to be characterized (CAP can form oligomers of different sizes). A tentative model of INF2 inhibition by KAC-actin–CAP can be proposed based on the results of A *et al.* [6], the crystal structures of some of the interacting components, and the homology between Dia1 and INF2 (Figure 1).

The large number of actin PTMs suggests that INF2 is not the only cytoskeletal protein whose activity is regulated in this manner. In addition, actin PTMs could regulate non-cytoskeletal processes, including nuclear processes such as chromatin remodeling [17]. It seems likely that these questions, and more, will stimulate a renewed interest in actin PTMs in future studies.

#### REFERENCES

- Dominguez, R. (2016). The WH2 domain and actin nucleation: necessary but insufficient. *Trends Biochem. Sci.* 41, 478–490.
- Breitsprecher, D., and Goode, B.L. (2013). Formins at a glance. *J. Cell Sci.* 126, 1–7.
- Song, Y., and Brady, S.T. (2015). Post-translational modifications of tubulin: pathways to functional diversity of microtubules. *Trends Cell Biol.* 25, 125–136.
- Magiera, M.M., Singh, P., Gadadhar, S., and Janke, C. (2018). Tubulin posttranslational modifications and emerging links to human disease. *Cell* 173, 1323–1327.
- Varland, S., Vandekerckhove, J., and Drazic, A. (2019). Actin post-translational modifications: the cinderella of cytoskeletal control. *Trends Biochem. Sci.*, pii: S0968-0004(18) 30259–7.
- A, M., Fung, T.S., Kettenbach, A.N., Chakrabarti, R., and Higgs, H.N. (2019). A complex containing lysine-acetylated actin inhibits the formin INF2. *Nat. Cell Biol.* 21, 592–602.
- Korobova, F., Ramabhadran, V., and Higgs, H.N. (2013). An actin-dependent step in mitochondrial fission mediated by the ER-associated formin INF2. *Science* 339, 464–467.
- Chakrabarti, R., Ji, W.K., Stan, R.V., de Juan Sanz, J., Ryan, T.A., and Higgs, H.N. (2018). INF2-mediated actin polymerization at the ER stimulates mitochondrial calcium uptake, inner membrane constriction, and division. *J. Cell Biol.* 217, 251–268.
- Madrid, R., Aranda, J.F., Rodriguez-Fraticelli, A.E., Ventimiglia, L., Andres-Delgado, L., Shehata, M., Fanayan, S., Shahheydari, H., Gomez, S., Jimenez, A., *et al.* (2010). The formin INF2 regulates basolateral-to-apical transcytosis and lumen formation in association with Cdc42 and MAL2. *Dev. Cell* 18, 814–827.
- Ramabhadran, V., Korobova, F., Rahme, G.J., and Higgs, H.N. (2011). Splice variant-specific cellular function of the formin INF2 in maintenance of Golgi architecture. *Mol. Biol. Cell* 22, 4822–4833.
- Chhabra, E.S., and Higgs, H.N. (2006). INF2 is a WASP homology 2 motif-containing formin that severs actin filaments and accelerates both polymerization and depolymerization. *J. Biol. Chem.* 281, 26754–26767.
- Ramabhadran, V., Hatch, A.L., and Higgs, H.N. (2013). Actin monomers activate inverted formin 2 by competing with its autoinhibitory interaction. *J. Biol. Chem.* 288, 26847–26855.
- Kotila, T., Kogan, K., Enkavi, G., Guo, S., Vattulainen, I., Goode, B.L., and Lappalainen, P. (2018). Structural basis of actin monomer re-charging by cyclase-associated protein. *Nat. Commun.* 9, 1892.
- Brown, E.J., Schlondorff, J.S., Becker, D.J., Tsukaguchi, H., Tonna, S.J., Uscinski, A.L., Higgs, H.N., Henderson, J.M., and Pollak, M.R. (2010). Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. *Nat. Genet.* 42, 72–76.
- Boyer, O., Nevo, F., Plaisier, E., Funalot, B., Gribouval, O., Benoit, G., Huynh Cong, E., Arrondel, C., Tete, M.J., Montjean, R., *et al.* (2011). INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. *N. Engl. J. Med.* 365, 2377–2388.
- Mattila, P.K., Quintero-Monzon, O., Kugler, J., Moseley, J.B., Almo, S.C., Lappalainen, P., and Goode, B.L. (2004). A high-affinity interaction with ADP-actin monomers underlies the mechanism and in vivo function of Srv2/cyclase-associated protein. *Mol. Biol. Cell* 15, 5158–5171.
- Kast, D.J., and Dominguez, R. (2011). Arp you ready for actin in the nucleus? *EMBO J.* 30, 2097–2098.

## Social Behaviour: Males Help When Mates Are Rare

Sjouke A. Kingma<sup>1,\*</sup> and Tamás Székely<sup>2,3,4,5</sup>

<sup>1</sup>Department of Animal Sciences, Behavioural Ecology Group, Wageningen University and Research, Wageningen, The Netherlands

<sup>2</sup>Milner Centre for Evolution, Department of Biology and Biochemistry, University of Bath, Bath, UK

<sup>3</sup>Department of Evolutionary Zoology and Human Biology, University of Debrecen, Egyetem tér 1, H-4032, Debrecen, Hungary

<sup>4</sup>Maio Biodiversity Foundation, Maio, Republic of Cape Verde

<sup>5</sup>Laboratory for Biodiversity Sciences and Ecological Engineering, College of Life Sciences, Beijing Normal University, Beijing 100875, China

\*Correspondence: [Sjouke.kingma@wur.nl](mailto:Sjouke.kingma@wur.nl)

<https://doi.org/10.1016/j.cub.2019.03.060>

In cooperatively-breeding animals, some individuals may postpone or completely forego independent reproduction to help others reproduce. A recent large-scale manipulation of adult sex ratio in wild nuthatches suggests that male birds postpone breeding because of a shortage of potential mates.

Cooperative breeding, whereby sexually mature individuals postpone reproduction and instead help another breeding pair to raise their young, occurs in a wide range of animals including humans, birds,

mammals and fishes [1]. Most notably, in many bird species helpers give up food that they could eat themselves to feed dependent offspring. Charles Darwin [2] was already puzzled by this seemingly

altruistic behaviour, and to this day, evolutionary biologists are still faced with the challenge of understanding why individuals would sacrifice their own reproduction to help others [1,3]. To solve





**Figure 1. Brown-headed nuthatches.**  
 Photo: David Blevins ([blevinsphoto.com](http://blevinsphoto.com)).

the puzzle, evolutionary and behavioural ecologists typically compare the benefit of helping others to the benefit of leaving home and trying to reproduce independently [1,3]. For example, subordinates may stay and help in their natal territory because family members allow them to use the resources on the territory [1,3]. A new study by James Cox and colleagues [4] opens an exciting line of investigation by showing that the decisions to help (or leave) are modulated by skewed sex ratios that reflect a shortage of mates.

Adult sex ratio is a central concept in population demography [5], and as the number of males and females influences the interactions between those of the same and opposite sex, the adult sex ratio is increasingly recognised as a demographic variable that can drive behavioural variability within and between the sexes [6,7]. Moreover, researchers are increasingly realising the potential of adult sex ratio in explaining social behaviours such as mate choice, pair-bonding and parenting [8,9]. In their new large-scale study, Cox and colleagues [4] highlight the role of adult sex ratio in cooperative breeding by testing whether the limited availability of mates due to skewed sex ratio may constrain young individuals to leave the family and breed independently. The ambitious field-based study of Cox and colleagues [4] provides experimental evidence that a shortage of potential

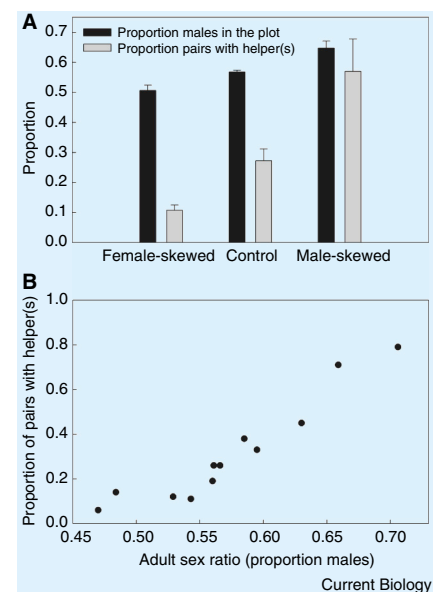
mates due to a skewed adult sex ratio leads to cooperative breeding, something that had never been observed at this scale before.

Cox and colleagues [4] investigated a small passerine bird, the brown-headed nuthatch (*Sitta pusilla*; Figure 1), that exhibits cooperative breeding. Instead of establishing a territory on their own, young nuthatches, nearly always males, sometimes help breeding pairs in their reproductive duties by feeding their new batch of young. Across several years, the researchers manipulated brood sex ratio in two forest plots. Male nestlings born in the first plot were swapped with females born in the second plot, resulting in a female-skewed and a male-skewed plot, respectively. This led to local populations with skewed adult sex ratios the year after.

The result of the experiment was profound: in the male-skewed plot, cooperative breeding became nearly twice as common as in a control plot where no manipulation took place. This was the result of young male nuthatches in male-skewed plots being more likely to stay and help to rear the young of others (Figure 2), presumably due to constrained mating opportunities. In the plots where male nestlings were removed, cooperative breeding became rare. Strikingly, the incidence of cooperative breeding was a direct function of the proportion of adult males in the population (Figure 2).

This experimental study complements a recent comparative analysis which found that helper sex ratio is related to adult sex ratio, likely due to mate shortages for the common sex [8]. The work of Cox and colleagues [4] goes beyond the comparative analysis by showing that the link between adult sex ratio and cooperative breeding is in fact causal — something that is difficult to determine in comparative analyses (Figure 2). To manipulate adult sex ratios in the nuthatch populations, the field team faced major challenges: first, male and female nuthatch young look identical, making it impossible to visually recognise nestlings that needed transferring to a different plot. The authors overcame this obstacle by using molecular markers to sex newly-hatched young; they teamed up with a local genetics laboratory that was capable of

providing the sex of offspring within a matter of days before moving male and female nestlings between plots as required. In addition, manipulating adult sex ratios in a wild population of birds or mammals requires huge effort, as it requires large-scale manipulation of the entire population. Cox and colleagues [4] overcame this hurdle by investigating an unusually large forest, 850 hectares in total. Local differences in habitat quality could be another pitfall for a well-designed experiment, because such characteristics could have driven the effects, rather than differences in adult sex ratio. The researchers elegantly circumvented the latter problem by reversing the sex-ratio skew between forest plots after two years of investigation: after a ‘wash-out’ year between the swaps when no manipulation took place, the experimental male-skewed plot became the female-skew targeted plot and *vice versa*; the effect appeared similar



**Figure 2. Sex ratio and cooperative breeding in brown-headed nuthatches.**  
 (A) Adult sex ratio (proportion males; black bars) and the proportion of pairs that have helpers (grey bars) in the years ( $n = 4$ ) after translocation of nestlings to female-skewed plots and male-skewed plots, and control plots. Error bars reflect standard errors over the four years. (B) The proportion of pairs with helpers appeared a direct result of skewed adult sex ratio (each dot reflects one plot in one year of study). Graphs were created using the data provided in Cox and colleagues [4].

regardless of where in the forest the male- and female-skewed populations were located. Finally, manipulating adult sex ratios in large populations of mobile organisms such as birds seems perilous, as the animals are likely to disperse and balance out the targeted local sex ratio biases. To some extent, this was the case for female-skewed plots (where females dispersed from them and consequently the adult sex ratio became close to even; [Figure 2](#)), but male brown-headed nuthatches did not disperse far, leading to heavily male-skewed plots.

Intriguingly, the presence of surplus males had a self-reinforcing effect: male offspring that hatched in the male-skewed plots were more likely to stay, and, surprisingly, male-skewed plots appeared to attract males from the outside. The result not only provides the key information that mate shortage leads to postponed independent breeding but also raises intriguing new questions: how do animals perceive skewed adult sex ratios? Do young

individuals use social information to help them decide whether to stay as subordinate in a group or disperse and become an independent breeder? The presence of surplus males may attract more males because in natural settings it would reflect a high-quality habitat. As nuthatch helpers are often unrelated to the family they join, the direct benefits of helping, such as access to food and mates and to a potential territory in the future, may thus be important drivers for individuals to stay and help. Therefore, Cox and colleagues [4] made a major step towards uncovering the role of a demographic trait (adult sex ratio) in a puzzling social behaviour (cooperative breeding), and their results open an exciting avenue for future research into how social information affects breeding systems.

#### REFERENCES

1. Koenig, W.D., and Dickinson, J. (2016). *Cooperative Breeding in Vertebrates: Studies of Ecology, Evolution and Behavior* (Cambridge: Cambridge University Press).
2. Darwin, C. (1859). *On the Origin of Species by Means of Natural Selection* (London: Murray).
3. Cockburn, A. (1998). Evolution of helping behavior in cooperatively breeding birds. *Annu. Rev. Ecol. Syst.* 29, 141–177.
4. Cox, J.A., Cusick, J.A., and DuVal, E.H. (2019). Manipulated sex ratios alter group structure and cooperation in the brown-headed nuthatch. *Behav. Ecol.* <https://doi.org/10.1093/beheco/arz030>.
5. Jennions, M., Székely, T., Bessinger, S., and Kappeler, P.M. (2017). Sex ratios. *Curr. Biol.* 27, R790–R792.
6. Székely, T., Weissing, F.J., and Komdeur, J. (2014). Adult sex ratio variation: implications for breeding system evolution. *J. Evol. Biol.* 27, 1500–1512.
7. Schacht, R., Kramer, K.L., Székely, T., and Kappeler, P.M. (2017). Adult sex ratios and reproductive decisions: a critical re-examination of sex differences in human and animal societies. *Philos. Trans. R. Soc. B* 372, 20160309.
8. Komdeur, J., Székely, T., Long, X., and Kingma, S.A. (2017). Adult sex ratios and the implications for cooperative breeding in birds. *Philos. Trans. R. Soc. B* 372, 20160322.
9. Liker, A., Freckleton, R.P., and Székely, T. (2013). The evolution of sex roles in birds is related to adult sex ratio. *Nat. Commun.* 4, 1587.

## Neuroscience: The Hidden Diversity of Electrical Synapses

Alberto E. Pereda

Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461, USA

Correspondence: [alberto.pereda@einstein.yu.edu](mailto:alberto.pereda@einstein.yu.edu)

<https://doi.org/10.1016/j.cub.2019.04.002>

The complete description of the expression of gap junction proteins in the nervous system of the worm reveals a great complexity of their distribution amongst different neuronal classes, opening an unprecedented opportunity to expose the functional diversity of electrical synapses.

Interconnected neurons communicate with each other at structures named synapses, where information is mediated via either the release of a transmitter substance ('chemical synapses') or the spread of electrical currents at a direct communicating pathway formed by aggregates of intercellular channels known as 'gap junctions' ('electrical synapses'), a prevalent form of signaling in neurons ([Figure 1A](#)). Chemical

synapses are known to be functionally diverse by combining different modalities of release, neurotransmitters and receptors. In contrast, the diversity of electrical synapses is less known. A potential mechanism for diversity in electrical synapses lies in the identity of the gap junction channel-forming proteins, named 'connexins' and 'innexins' in vertebrates and invertebrates, respectively [1]. Since the

intercellular channel is formed by the docking of two channels, or 'hemichannels', each provided by one of the contacting cells, it is possible to have intercellular channels made by hemichannels formed by a single protein (homotypic intercellular channel), two different proteins (heterotypic intercellular channel) or by heteromeric channels in either homotypic or heterotypic configurations ([Figure 1B](#)) [2].

