proteins and components of the quality control system to allow either refolding or proteolytic degradation. Since JUNQ and IPOD are at least partially dynamic it would be worth knowing if aggregate formation is a reversible process. Finally, the important observation that cytosolic and amyloidogenic proteins are differentially transported to distinct quality control compartments allows for a better understanding of the basic mechanisms and development of protein conformation diseases.

References
1. Morimoto, R.I., Kline, M.P., Bimston, D.N., and Cotto, J.J. (1997). The heat-shock response: regulation and function of heat-shock proteins and molecular chaperones. Essays Biochem. *32*, 17–29.
2. Hershko, A., and Ciechanover, A. (1998). The ubiquitin system. Annu. Rev. Biochem. *67*, 425–479.
3. Hochstrasser, M. (1996). Ubiquitin-dependent protein degradation. Annu. Rev. Genet. *30*, 405–439.
4. Arrasate, M., Mitra, S., Schweitzer, E.S., Segal, M.R., and Finkbeiner, S. (2004). Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature *431*, 805–810.
5. Kaganovich, D., Kopito, R., and Frydman, J. (2008). Misfolded proteins partition between two distinct quality control compartments. Nature *454*, 1088–1095.
6. Parsell, D.A., Kowal, A.S., Singer, M.A., and Lindquist, S. (1994). Protein disaggregation mediated by heat-shock protein Hsp104. Nature *372*, 475–478.
7. Glover, J.R., and Lindquist, S. (1998). Hsp104, Hsp70, and Hsp40: A novel chaperone system that rescues previously aggregated proteins. Cell *94*, 73–82.
8. Goloubinoff, P., Mogk, A., Zvi, A.P., Tomoyasu, T., and Bukau, B. (1999). Sequential mechanism of solubilization and refolding of stable protein aggregates by a bichaperone network. Proc. Natl. Acad. Sci. USA *23*, 13732–13737.
9. Muchowski, P.J., and Wacker, J.L. (2005). Modulation of neurodegeneration by molecular chaperones. Nat. Rev. Neurosci. *6*, 11–22.
10. Iwata, A., Christianson, J.C., Bucci, M., Ellerby, L.M., Nukina, N., Forno, L.S., and Kopito, R.R. (2005). Increased susceptibility of cytoplasmic over nuclear polyglutamine aggregates to autophagic degradation. Proc. Natl. Acad. Sci. USA *102*, 13135–13140.
11. Rideout, H.J., Lang-Rollin, I., and Stefanis, L. (2004). Involvement of macroautophagy in the dissolution of neuronal inclusions. Int. J. Biochem. Cell. Biol. *36*, 2551–2562.
12. Johnston, J.A., Ward, C.L., and Kopito, R.R. (1998). Aggresomes: A cellular response to misfolded proteins. J. Biol. Chem. *143*, 1883–1898.
13. Iwata, A., Riley, B.E., Johnston, J.A., and Kopito, R.R. (2005). HDAC6 and microtubules are required for autophagic degradation of aggregated Huntingtin. J. Biol. Chem. *280*, 40282–40292.
14. Kopito, R.R. (2000). Aggresomes, inclusion bodies and protein aggregation. Trends Cell Biol. *10*, 524–530.
15. Huyer, G., Longsworth, G.L., Mason, D.L., Mallampalli, M.P., McCaffery, J.M., Wright, R.L., and Michaelis, S. (2004). A striking quality control subcompartment in Saccharomyces cerevisiae: the endoplasmic reticulum-associated compartment. Mol. Biol. Cell. *15*, 908–921.

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Social Evolution: This Microbe Will Self-Destruct

Phenotypic noise and social evolution in microbes have recently attracted huge interdisciplinary interest. A new study highlights the interaction between these phenomena and its implications for self-destructive cooperation.

Andy Gardner and Rolf Kümmerli

The traditional view of the microbe is of a simple automaton, blindly following its genetic programming. This appears to leave little room for personal idiosyncrasies, let alone a social life. However, this view of the microbe as a generic loner has been increasingly challenged in recent years, which have seen an explosion of research on the topics of bacterial individuality and social behaviour.

Phenotypic noise is an inescapable fact of life. Although biologists commonly speak of a gene 'for' a particular trait, this is only ever intended in a statistical sense. Phenotypes vary even in the absence of genetic differences between individuals, and the phenomenon of bi-stability, whereby genetically-identical cells exhibit dramatically different phenotypes, has been of particular recent interest [1–3]. An example is bacterial persistence [4], whereby a fraction of cells enter a non-growing phase during which they are refractory to antibiotics. The quiescent cells that survive antibiotic treatment give rise to growing populations that exhibit no reduction in their antibiotic susceptibility, supporting the idea that they are genetically indistinguishable from cells that are killed. In many cases, bi-stability appears to emerge spontaneously, and a plausible mechanism for this differentiation is the coupling of stochastic gene expression with positive-feedback mechanisms, so that random noise at the molecular level is converted into distinct cell types at the phenotypic level [1].

In parallel to this work on bi-stability, there has been much recent interest in the social lives of microbes [5,6]. Here, the problems faced by human society are recast in miniature. Of particular interest is the question of why individuals should contribute effort for the greater public good, when this leaves them at a disadvantage relative to 'free-riders' who exploit the cooperation of others while giving nothing in return. For example, bacterial growth is often limited by access to iron, and cells that produce iron-scavenging molecules called siderophores help to increase the availability of iron for themselves and others; however, siderophores are costly to produce, and cooperative cells are in danger of being outcompeted by cheaters who invest nothing into this public good [7]. A major explanation for the survival of selflessness is kin selection [8]. Although cooperation can incur a personal cost, the gene for cooperation might enjoy an overall benefit if the public-good contributions accrue preferentially to relatives of the cooperator, who tend to carry copies of the same gene.

In a recent study, Ackermann et al. [9] combined the concepts of phenotypic noise and public-goods cooperation to study drastic cooperative behaviours that lead to a total loss of reproductive success for the cooperator. From a genetic-determinism point of view, such self-destructive cooperation is very puzzling: a gene that leads all its carriers to make the ultimate sacrifice should become extinct in a single
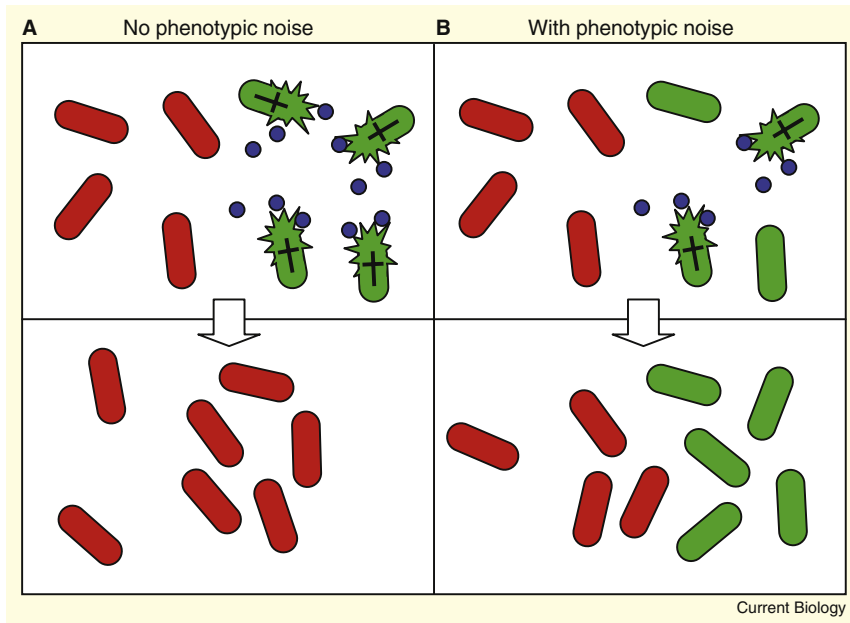
Figure 1. Evolutionary scenarios for two generations in populations of bacteria that carry the gene for self-destructive cooperation (green cells) and bacteria that do not (red cells).

(A) Without phenotypic noise, all carriers of the cooperation gene self-destruct thereby releasing a public good (blue dots), and cooperation becomes extinct in a single generation. (B) With phenotypic noise, not all of the carriers of the cooperative gene self-destruct, so that cooperation can persist, and even be selectively favoured by kin selection, as bacteria grow to higher density in the vicinity where self-destructive cooperation happened.

generation. Yet, such feats of cooperation do occur in microbial populations. In *Streptococcus pneumoniae* infections, some bacterial cells release a toxin called pneumolysin by self-destructive bursting, which promotes the invasion of the lung by cells that refrain from this extreme behaviour. As a solution to this problem, Ackermann *et al.* [9] propose that phenotypic noise ensures that only a certain proportion of carriers of the cooperation gene will exhibit self-destructive behaviour. This bi-stability ensures that there will be carriers of the cooperation gene among the beneficiaries of the public good, and hence the suicidal act could be favoured by kin selection (Figure 1).

As with many compelling evolutionary arguments, this idea has its roots in *The Origin of Species* [10], in a passage in which Charles Darwin tackled the problem of sterile workers in social-insect colonies. Darwin noted that, although workers do not enjoy any personal reproduction, their behaviour in the colony is beneficial to family members who are fertile, and he suggested that these reproductives carry an unexpressed tendency for the sterile condition, and pass it to their offspring, ensuring the presence

of workers in future generations. This has since been verified: genetically identical eggs can develop either as reproductives or as workers, depending on extrinsic factors [11]. Darwin's hypothesis laid the initial foundations of kin-selection theory that was to be developed thoroughly by William Hamilton [8] more than a century later. Later still, Brian Charlesworth [12,13] returned to the particular problem of self-destructive cooperation in social insects, providing an exact population-genetic analysis which confirmed that altruism evolves more readily if the probability of gene expression is lowered. Charlesworth showed that selection often favours a reduced phenotypic penetrance of the gene, while also increasing the level of altruism exhibited by those who do express it, leading ultimately to a sterile caste that is genetically indistinguishable from the colony's reproductives.

Ackermann *et al.* [9] have developed this theory of self-destruction for special application to microbes. Their mathematical model describes bacterial social neighbourhoods within which cells are genetically related due to recent coancestry and it confirms that, while an obligately expressed

gene for self-destructive behaviour can never be favoured, kin selection does favour those genetic lineages in which only a fraction of cells express extreme cooperation. The greater the degree of relatedness, and the larger the benefit to the other cells in the neighbourhood, the higher the predisposition for suicidal cooperation will be. The researchers then tested the three main assumptions of their model, using *Salmonella typhimurium* infections in mice. These bacteria induce an inflammatory response in the gut tissue mediated by a fraction of bacteria producing virulence factors, mainly through type-III secretion systems (TTSS) and through flagella gene expression, which serves to eradicate resident microflora, and hence facilitates their own successful establishment in the gut lumen [14,15].

TTSS expression and its associated invasion of the gut tissue appears to be very costly for the invading cells but provides a benefit for the infection as a whole. Ackermann *et al.* [9] confirmed first, there is phenotypic variability in TTSS expression in clonal populations of *S. typhimurium*; second, that TTSS expression is required for invasion of host tissue, and is correlated with inflammation; and third, that a high proportion of TTSS-expressing cells are killed by host defences. Thus, TTSS-mediated invasion of the gut tissue is essentially a suicidal trait that appears to be favoured because it provides a public good that is enjoyed by the altruistic cell's close kin.

This work highlights a useful synergy between the topics of phenotypic noise and social evolution in microbes, and provides further support for the view that these phenomena are of medical and veterinary importance. On the particular issue of self-destructive cooperation, however, some basic issues remain unresolved. While genetic relatedness is undoubtedly important in explaining suicidal cooperation, it is not the whole solution. Population processes that generate relatedness between neighbours (such as limited mixing of individuals between social groups) can intensify competition between social partners, negating the benefits of cooperation [16]. Hence, a proper understanding of microbial ecology will be crucial in resolving this problem. Also, while there has been a tendency

to focus on stochastic sources of phenotypic differentiation, it is difficult *a priori* to rule out other explanations. For example, there may be a role for signaling in deciding which cells will express the self-destructive phenotype [17]. Alternatively, microbes might be responding to differences in their personal quality: a moribund cell with nothing to lose will be more inclined towards committing suicide for the good of its healthy neighbours. More sinister is the possibility that bacteria are manipulated into making the sacrifice; such coercion is observed in insect colonies [18]. To understand why microbes take the ultimate plunge, we should first ask: did they jump, or were they pushed?

References
1. Kaern, M., Elston, T.C., Blake, W.J., and Collins, J.J. (2005). Stochasticity in gene expression: from theories to phenotypes. Nat. Rev. Microbiol. *6*, 451–462.
2. Dubnau, D., and Losick, R. (2006). Bistability in bacteria. Mol. Microbiol. *61*, 564–572.
3. Veening, J.-W., Smits, W.K., and Kuipers, O.P. (2008). Bistability, epigenetics, and bet-hedging in bacteria. Annu. Rev. Microbiol. *62*, 193–210.
4. Lewis, K. (2007). Persister cells, dormancy and infectious disease. Nat. Rev. Microbiol. *5*, 48–56.
5. Crespi, B.J. (2001). The evolution of social behavior in microorganisms. Trends Ecol. Evol. *16*, 178–183.
6. West, S.A., Griffin, A.S., Gardner, A., and Diggle, S.P. (2006). Social evolution theory for microorganisms. Nat. Rev. Microbiol. *4*, 597–607.
7. West, S.A., and Buckling, A. (2003). Cooperation, virulence and siderophore production in bacterial parasites. Proc. R. Soc. Lond. B *270*, 37–44.
8. Hamilton, W.D. (1964). The genetical evolution of social behaviour. J. Theor. Biol. *7*, 1–52.
9. Ackermann, M., Stecher, B., Freed, N.E., Songhet, P., Hardt, W.-D., and Doebeli, M. (2008). Self-destructive cooperation mediated by phenotypic noise. Nature *454*, 987–990.
10. Darwin, C.R. (1859). The Origin of Species (London: John Murray).
11. Wheeler, D.E. (1986). Developmental and physiological determinants of caste in social Hymenoptera: evolutionary implications. Am. Nat. *128*, 13–34.
12. Charlesworth, B. (1978). Some models of the evolution of altruistic behaviour between siblings. J. Theor. Biol. *72*, 297–319.
13. Charlesworth, B. (1980). Models of kin selection. In Evolution of Social Behaviour: Hypotheses and Empirical Tests, H. Markl, ed. (Weinheim: Verlag Chemie), pp. 11–26.
14. Stecher, B., Hapfelmeier, S., Müller, C., Kremer, M., Stallmach, T., and Hardt, W.-D. (2004). Flagella and chemotaxis are required for efficient induction of *Salmonella enterica* serovar Typhimurium colitis in streptomycin-pretreated mice. Infect. Immun. *72*, 4138–4150.
15. Stecher, B., Robbiani, R., Walker, A.W., Westendorf, A.M., Barthel, M., Kremer, M., Chaffron, S., Macpherson, A.J., Buer, J., Parkhill, J., *et al*. (2007). *Salmonella enterica* serovar Typhimurium exploits inflammation to compete with the intestinal microbiota. PLoS Biol. *5*, e244.
16. Taylor, P.D. (1992). Altruism in viscous populations - an inclusive fitness model. Evol. Ecol. *6*, 352–356.
17. Keller, L., and Surette, M.G. (2006). Communiction in bacteria: an ecological and evolutionary perspective. Nat. Rev. Microbiol. *4*, 1–11.
18. Wenseleers, T., and Ratnieks, F.L.W. (2006). Enforced altruism in insect societies. Nature *444*, 50.

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