Supplementary Material:

TOWARDS AN EVOLUTIONARY THEORY OF STRESS RESPONSES

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Table S1: Mechanisms of stress responses across major organismal groups

Clade	Process	Stress molecules	Molecular trigger	Release from	Receptors for stress molecules	Negative feedback	Function	References
Animals, Vertebrates	Fast wave	Noradrenaline, serotonin (5-HT), dopamine	Directly by brain circuits involved in evaluation of stressor, or indiretly through activation of sympathetic nervous system (SNS)	Neurons	Adrenergic receptors α1 and 2 and β (noradrenaline), 5-HT1, 2 and 7 receptors (serotonin), D1 and D2 receptors (dopamine); all receptors have several subtypes		Promote vigilance, alertness, appraisal of situation and choice of optimal strategy to cope with stressor, learning, regulation of immune system	Joels & Baram 2009, Padro & Sanders 2014, Ulrich-Lai & Herman 2009
Animals, Vertebrates	Slow wave	Glucocorticoids (Cortisol, Corticosterone)	ACTH	Adrenal gland (mammals), interrenal gland (fish)	Mineralocorticoid (MR) and glucocorticoid receptors (GR), corticotropin-releasing hormone receptor 2 (CRHR2)	Binding of CORT to receptors GR and CRHR2	Transcription factor for nucleic genes; sustained, adaptive components of stress response (consolidation of information, memory formation)	Joels & Baram 2009
Animals, Molluscs		Noradrenaline, (Dopamine)	ACTH	Neuroendocrine cells similar to vertebrate chromaffin cells	α- and β-adrenoceptors	-	-	Lacoste et al. 2001a,b,c
Animals, Insects	Fast wave	Octopamine		Neurons	α-adrenergic-like and β-adrenergic like octopamine receptors		Release of lipid from fat stores and sharpens sensory responsiveness	Adamo et al. 2013, Adamo & Baker 2011, Evans & Maqueira 2005
Animals, Insects	Slow wave	Adipokinetic hormone, AKH	-	Endocrine gland (corpora cardiacum)	AKH receptors	-	Regulating fuel transport in the haemolymph, for redirecting energy to processes required due to stress	Adamo et al. 2013, Adamo & Baker 2011, Staubli et. al 2002
Plants, Cormophytes (osmotic stress)		Terpenoid hormones (Abscisic acid,ABA)	Enzyme NCED (9-cisepoxycarotenoid dioxygenase)	Roots, leaves, stem and flowers	Cheletase (ChlH), G-protein coupled receptor Type G-proteins (GTGs), and Pyrabactin resistant/Pyrabactin resistant–like/Regulatory component of ABA receptor (PYR/PYL/RCAR receptors)	ABA promotes formation of AREB1/NAC2 protein complex, which inhibits NCED transcription	Closing of stomata; providing energy by degrading starch; ABA induces expression of stress genes	Cutler et al. 2010, Hartung 2010, Liu et al. 2016, Thalmann et al. 2016,
Fungi, Yeast		Expression of ca 200 'stress genes'	Proteins Msn2 and Msn4	Nucleus	Msn2, Msn4	By degradation of Msn2	-	Bose et al. 2005

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Part 2:

DETAILED MODEL DESCRIPTION

1. Basic scenario

We model a prey animal living in an environment that, at any given moment in time, is in one of two possible states: a threat (e.g. a predator) is either nearby and close enough to launch an attack, or it is further away and beyond the attack range. Time is divided into discrete steps (representing short intervals on the order of minutes) and movement of the predator is governed by an autocorrelated process, with transition probabilities λ_L and λ_A specifying the chance (from one time step to the next) that the predator leaves the vicinity (given that it is present) or arrives (given that it is absent), respectively. If $\lambda_A + \lambda_L < 1$ there is positive temporal autocorrelation, so that if the predator is present in a given time step, its probability of being present in the next time step is higher than the average probability, which is equal to $\lambda_A/(\lambda_A + \lambda_L)$. This average probability is equal to the level of risk, as it reflects the overall long-term proportion of time for which the threat is present. The prey animal is unable to detect that the predator is nearby until it attacks. If the predator is nearby it attacks with probability p_{att} at the start of the time step, killing the prey with probability p_{kill}. There is also a background probability of mortality μ per time step from factors unrelated to predation.

If the prey animal successfully avoids both background mortality and mortality due to predation, it produces r offspring in that time step and can then mount a stress response to protect itself against a possible attack at the start of the next time step. Specifically, in the next time step it expresses a stress hormone at level $h(\tau)$ (with $0 \leq h(\tau) \leq 1$), where τ represents the number of time steps $\tau = 1, 2, 3, \ldots$ since it last experienced an attack (note that $\tau = 1$ implies that an unsuccessful attack occurred in the previous time step). We assume that increasing h reduces both p_{kill} and r (and hence there is a cost–benefit trade-off), according to the following functions:

$$p_{kill}\left(h(\tau)\right) = 1 - h(\tau)^{\alpha} \quad (1)$$

$$r\left(h(\tau)\right) = 1 - h(\tau)^{\beta} \tag{2}$$

where α and β are constants that control whether the dependence on h is decelerating, linear or accelerating.

2. Optimal strategy

We can use state-dependent dynamic programming to find the optimal hormone $h^{*}(\tau)$ for all τ; this is the strategy that maximises total lifetime reproductive output. At τ time steps after the last attack, the probability a predator is present, p_{pred}, is given by:

$$p_{\text{pred}}(\tau) = 1 - \lambda_{\text{L}} \qquad \text{for } \tau = 1 \tag{3}$$

$$p_{\text{pred}}(\tau) = \frac{p_{\text{pred}}(\tau - 1) \cdot (1 - p_{\text{att}}) \cdot \left(1 - \lambda_{\text{L}}\right) + \left(1 - p_{\text{pred}}(\tau - 1)\right) \cdot \lambda_{\text{A}}}{1 - p_{\text{pred}}(\tau - 1) \cdot p_{\text{att}}} \qquad \text{for } \tau > 1 \tag{4}$$

Equation (4) above represents the conditional probability that a predator is present given that there was no attack in the previous time step (i.e. $\tau - 1$ time steps after the last attack). The first term in the numerator is the probability that a predator was present in the previous time step but did not attack $(1 - p_{\text{att}})$ and did not leave the vicinity $(1 - \lambda_{\text{L}})$; the second term is the probability that no predator was present in the previous time step but one has since arrived (λ_{A}). The denominator is the overall probability that no attack occurred in the previous time step.

At the start of a time step, the expected fitness W of the prey animal if it expresses hormone level h is then

$$\begin{aligned} W\left(\tau\right) = {} & p_{\text{pred}}(\tau) \cdot p_{\text{att}} \cdot \left[1 - p_{\text{kill}}\left(h(\tau)\right)\right] \cdot (1 - \mu) \cdot \left[r\left(h(\tau)\right) + W'(1)\right] \\ & + \left(1 - p_{\text{pred}}(\tau) \cdot p_{\text{att}}\right) \cdot (1 - \mu) \cdot \left[r\left(h(\tau)\right) + W'\left(\tau + 1\right)\right] \end{aligned} \tag{5}$$

where W' denotes its expected fitness in the next time step (assuming it continues to follow the same strategy). Equation (5) captures the two possible outcomes where the animal

survives the current time step: either it is attacked ($p_{\text{pred}} \times p_{\text{att}}$) but not killed by the predator ($1 - p_{\text{kill}}$) nor by background mortality ($1 - \mu$), in which case τ is reset to 1 in the next time step; or it is not attacked ($1 - p_{\text{pred}} \times p_{\text{att}}$) and it successfully avoids background mortality ($1 - \mu$), in which case τ is incremented by one time step. In both cases its fitness comprises the r offspring produced in the current time step plus its expected fitness in the next time step (as a function of the updated value of τ).

The optimal strategy is that which maximises W over possible values of h:

$$h^*(\tau) = \max_h \left[W(\tau) \right] \tag{6}$$

This is found iteratively by setting an arbitrary terminal reward function, e.g. $W'(\tau) = 1$ for all h, then calculating backwards through time until $h(\tau)$ converges on a stable solution $h^*(\tau)$, where the change in fitness $|W' - W|$ between successive iterations is below some small amount (e.g. 0.000001). Note that this solution is independent of time (so it is valid for all time steps) and is also unaffected by the terminal reward function (since background mortality ensures that the animal has negligible chance of surviving that long).

3. Mechanistic evolutionary simulation

For the same scenario, we simulated the evolution of a specific physiological mechanism that controls the dynamics of the stress hormone. In a given time step t, the stress hormone concentration h_t in an individual prey animal is given by

$$h_t = I + \delta S + (1 - C) h_{t-1} \tag{7}$$

where I, S and C are the values of three evolvable traits represented by unlinked diploid genetic loci: I ($I \geq 0$) specifies the baseline influx of stress hormones per time step when no predatory attack occurs; S ($S \geq 0$) specifies an additional stress-induced influx in response to a predatory attack (δ is Kronecker's delta, with $\delta = 1$ in time steps where an attack occurs and $\delta = 0$ otherwise); and C ($C_{\min} \leq C \leq 1$) specifies the rate of clearance of hormones present in the preceding time step $t - 1$. Here, $C_{\min} > 0$ is a parameter that reflects the minimum rate

of hormone clearance, to prevent the biologically unrealistic scenario of $C = 0$ in which clearance would be absent and stress hormones would never be excreted or degraded. Finally, initial stress hormone levels at the start of an individual's life are given by another evolving locus H_0.

We simulate an evolving population of N prey animals with these four unlinked traits I, S, C and H_0, where predatory attacks on any one individual are assumed to occur independently of those on other prey. Each time step, those individuals killed by predators or background mortality are replaced by an equal number of offspring through sexual reproduction, to maintain a constant population size. For each offspring produced in time step t, two parents are randomly selected from the population of surviving adults with a chance proportional to their reproductive propensity r in that time step, which is a function of their current hormone level (see equation (2) above). An offspring inherits one allele from its mother and one allele from its father for each locus, which contribute additively to each trait (i.e. there is no dominance/epistasis). After inheritance each allele then mutates with probability v per generation, in which case the allelic value is incremented by an amount drawn from a normal distribution with mean 0 and variance σ_v^2. If mutation pushes the allelic value outside the allowable range for that trait, it is reset to the nearest value within the range.

The parameter values used for the simulation results shown in Box 3 were as follows: $N = 5000$, $v = 0.005$, $\sigma_v^2 = 4 \times 10^{-4}$, $\alpha = 1.0$, $\beta = 1.5$, $p_{\text{att}} = 0.5$, $\mu = 0.002$. The transition probabilities used were: (A) $\lambda_A = 0.05$, $\lambda_L = 0.95$ (implying overall risk 0.05 and autocorrelation 0); (B) $\lambda_A = 0.035$, $\lambda_L = 0.665$ (implying overall risk 0.05 and autocorrelation 0.3); (C) $\lambda_A = 0.1$, $\lambda_L = 0.9$ (implying overall risk 0.1 and autocorrelation 0); and (D) $\lambda_A = 0.005$, $\lambda_L = 0.095$ (implying overall risk 0.05 and autocorrelation 0.9). Varying the mutation rate v typically does not change the main results, but it does affect the speed with which the various traits reach their equilibria and the amount of genetic variation present in the population. The models were written in C++ and are available on github: (https://github.com/bramkuijper/stress/tree/master/src/ibm).

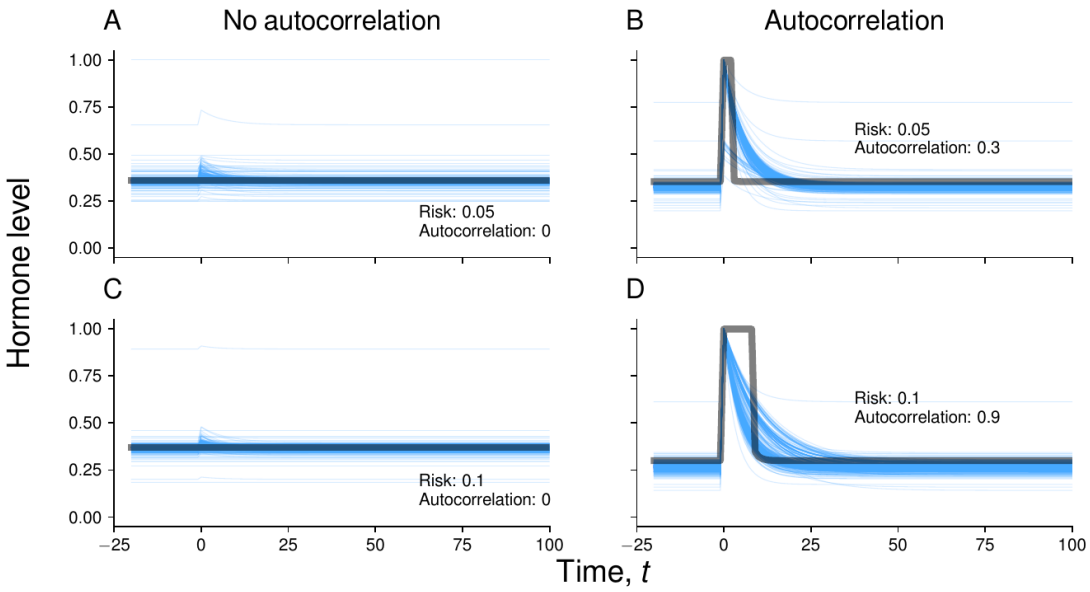

Figure S1. Evo-mecho predictions for the stress response when maximal fecundity *r*(*h*) occurs for an intermediate hormone level (rather than when *h*=0). Fecundity is given by the parabolic function $r(h) = 1 - c_r(h - \theta_r)^2$. While the effect of risk is less pronounced than for the case in Figure I of Box 3 in the main text, the difference between autocorrelated and random environments remains pronounced. Parameters: $c_r = 4, \theta_r = 0.2$.