Development and Selective Grain Make Plasticity ‘Take the Lead’ in Adaptive Evolution

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Research article

Keywords: Adaptation, Phenotypic plasticity, Genotype-phenotype-map, Plasticity-led evolution, Parental effects, Mechanistic developmental models

Posted Date: May 24th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-495293/v1>

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1 Development and selective grain make plasticity ‘take the lead’ in adaptive evolution

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9

10 Abstract

11

12 **Background:** Biological evolution exhibits an extraordinary capability to adapt organisms to their
13 environments. The explanation for this often takes for granted that random genetic variation
14 produces at least some beneficial phenotypic variation in which natural selection can act. Such
15 genetic evolvability could itself be a product of evolution, but it is widely acknowledged that the
16 immediate selective gains of evolvability are small on short timescales. So how do biological
17 systems come to exhibit such extraordinary capacity to evolve? One suggestion is that adaptive
18 phenotypic plasticity makes genetic evolution find adaptations faster. However, the need to explain
19 the origin of adaptive plasticity puts genetic evolution back in the driving seat, and genetic
20 evolvability remains unexplained.

21 **Results:** To better understand the interaction between plasticity and genetic evolvability, we
22 simulate the evolution of phenotypes produced by gene-regulation network-based models of
23 development. First, we show that the phenotypic variation resulting from genetic and environmental
24 perturbation are highly concordant. This is because phenotypic variation, regardless of its cause,
25 occurs within the relatively specific space of possibilities allowed by development. Second, we
26 show that selection for genetic evolvability results in the evolution of adaptive plasticity and *vice*
27 *versa*. This linkage is essentially symmetric but, unlike genetic evolvability, the selective gains of
28 plasticity are often substantial on short, including within-lifetime, timescales. Accordingly, we show
29 that selection for phenotypic plasticity can be effective in promoting the evolution of high genetic
30 evolvability.

31 **Conclusions:** Without overlooking the fact that adaptive plasticity is itself a product of genetic
32 evolution, we show how past selection for plasticity can exercise a disproportionate effect on
33 genetic evolvability and, in turn, influence the course of adaptive evolution.

34

35 **Keywords:** Adaptation, Phenotypic plasticity, Genotype-phenotype-map, Plasticity-led evolution,
36 Parental effects, Mechanistic developmental models

37 **Background**

38

39 Understanding how evolution works is not complete by understanding natural selection; we
40 also need to understand the generation of the phenotypic variation that natural selection will act on
41 [1,2]. While the genetic variation that makes evolution possible is essentially non-directional (i.e.
42 random mutations), the phenotypic variation that results from these genetic changes is highly
43 structured, causing some variants to appear more frequently than others [3-5]. This directional
44 phenotypic variation arises because of the complex process of development, and is hence commonly
45 known as “developmental bias” [6,7]. If this developmental bias is aligned with the adaptive
46 demands imposed by local environments (i.e., if the mutationally more accessible phenotypes are
47 also the more adaptive ones), adaptive evolution would be greatly facilitated. Here, we refer to this
48 as a situation with high genetic evolvability, whereas a situation where adaptive phenotypes would
49 be total or partially inaccessible through mutation represent low genetic evolvability.

50 The developmental origins of genetic evolvability, and the causes and consequence of its
51 evolution, have generated much interest and controversy, not least over the past decade [6,7]. One
52 reason for the controversy is that it is unclear why developmental systems should exhibit facilitated
53 variation. Genetic evolvability could itself be a product of past evolution [7-9], but the idea that
54 natural selection would be able to improve genetic evolvability is problematic because the
55 immediate selective gains of responding adaptively to random genetic change are small on short
56 timescales [9,10].

57 Another suggestion is that the high genetic evolvability is acquired through the capability of
58 organisms to rapidly adapt to their environment during their lifetime [11]. However, while adaptive
59 plasticity often appears to ‘take the lead’ in adaptive evolution (e.g., [12,13]), the idea that adaptive
60 plasticity explains genetic evolvability overlooks the need to explain the origination of the adaptive
61 plasticity that supposedly ‘came first’. In this paper, we seek to better understand whether
62 phenotypic plasticity can help to explain genetic evolvability without overlooking the fact that
63 adaptive plasticity is itself a product of genetic evolution [14].

64 The starting point of our approach is grounded on previous theoretical and empirical
65 observations which suggest that the phenotypic consequences of genetic variation and
66 environmental variation are not independent [12,14-18]. Such non-independence is indeed
67 expected, because the consequences of any perturbation of development will be channelled by the
68 same underlying developmental mechanisms [19]. From this, it follows that, if selection for
69 phenotypic plasticity alters the structure of developmental interactions, this will likely alter how
70 phenotypes respond to genetic mutations and hence affect evolvability. Population genetic models
71 demonstrate that selecting for plasticity can increase genetic variation along the dimensions of the

72 phenotype that are plastic [20,21]. This seems to support a role for plasticity in shaping genetic
73 evolvability. However, given that the interdependence of plasticity and evolvability on development
74 is essentially symmetric (i.e. both covary as a result of a common developmental dynamics, but
75 none is cause or consequence of the other), the reverse may be equally possible. That is, if selection
76 on genetic evolvability alters the structure of developmental interactions, this should also alter how
77 phenotypes respond to environmental variation. It thus remains an open question whether genetic
78 evolvability is predominantly shaped by plasticity or *vice versa* [14,22].

79 To address this question, we study the relationship between plasticity and evolvability by
80 representing these phenomena in a common framework where the phenotypic effects and adaptive
81 consequences of genetic and environmental variation can be compared. The phenotype distribution
82 that is generated by genetic variation can be represented as a genotype-phenotype (GP) map: an
83 idealized representation of development that assigns a phenotype to each genotype [3,6,22]. If the
84 main axis of the phenotypic distribution showed by the GP map is aligned with the adaptive
85 demands, then phenotypes that are suitable for adaptation arise more readily, and the GP map is said
86 to exhibit high genetic evolvability [9].

87 Analogous to the GP map, plasticity can be understood as an Environment-Phenotype (EP)
88 map (aka reaction norm) that associates each environment with its corresponding phenotype
89 [23,24,25]. Plasticity is adaptive when the EP map enables individuals to produce phenotypes that
90 fit the requirements of the environment in which they find themselves. However, the GP and EP
91 maps do not exhaust the sources of phenotypic variation. Development is also sensitive to non-
92 genetic and non-environmental initial conditions such as biochemical templates, resources and
93 nutrients that are provided by the parents [26,27]. The association of such elements with phenotypic
94 variation is often referred to as parental effects [28]. Here we emphasize the analogous role of such
95 initial conditions in structuring the phenotype distribution by referring to it as the PP (for ‘Parental-
96 Phenotype’) map: a mapping that associates a phenotype with the parentally inherited initial
97 conditions required to produce it. Notice that, although “maps” are formal mathematical objects, we
98 adopt here a more flexible use of the term, equating it to the phenotypic distributions arising from a
99 specific type of parametric perturbations.

100 To model the potential interdependence of these three maps (GP, EP and PP), we use several
101 different and widely used models of development based on gene regulatory networks (GRN). This
102 approach means that we neither assume that the three maps are independent nor that they are
103 related; rather, these are hypotheses we can test. To do this we apply the three different forms of
104 variation (i.e. genetic, environmental, parental) to the core GRNs of the developmental system we
105 use, and compare the resulting phenotypic effects to see if they are similar or not.

106 In principle, it could be the case that any concordance between the three maps in this model
 107 could be intrinsic to the properties of GRNs and arise without selection, or observed only in GRNs
 108 subjected to particular selective conditions, or not observed at all. Likewise, it is not known whether
 109 selection can, for example, change the GP map produced by a GRN without altering the EP or PP
 110 maps, or more generally, whether the effects of selecting for one map has consequences for the
 111 properties of the others. Lastly, even if it is the case that selection for one map can determine the
 112 evolution of any other map, it could be the case that one of the maps is easier to change with
 113 selection than the others. Therefore, the aims of this paper are 1) to assess the potential
 114 interdependence of the GP, EP and PP maps; 2) to determine how (and if) the evolution of one map
 115 affects the evolution of the others, and whether this evolution is symmetric; and 3) to establish
 116 whether or not the three maps are equally responsive to selection.

117

118 **Results:**

119

120 To model how the GP, EP and PP maps interact, it is necessary to represent developmental
 121 systems in a way that allow for genetic, environmental and parental inputs. We expand on three
 122 different and widely used GRN-based models of development, each one entailing a different
 123 complexity and biological realism (Fig. 1A-C). To better interpret our results, we succinctly
 124 introduce here the architecture of the models we use (see Methods section for further details). From
 125 the simpler to the more complex, these models are:

126

127 **-Basic GRN model.** This model (based on [29]) represents a simple gene regulatory network
 128 (GRN; Fig. 1A). It consists of N_g transcription factors that have continuous, positive concentrations
 129 (vector $G=(g_1, \dots, g_{N_g})$; $g_i \geq 0 \ \forall \ i$), and regulate the expression of each other by binding to cis-
 130 regulatory sequences on gene promoters. The regulatory interactions of this GRN are encoded in the
 131 $N_g \times N_g$ matrix B , whose elements B_{ik} represent the effect of gene k on the transcription of gene i .
 132 Positive elements ($B_{ik} > 0$) represent activation and negative elements ($B_{ik} < 0$) represent inhibition. A
 133 binary (0 or 1) matrix M ($N_g \times N_g$) encodes the GRN topology, so that the interaction B_{ik} is only
 134 active if $M_{ik}=1$. The initial state of the vector G (represented by the vector G_0) accounts for the
 135 initial state at the beginning of development, which is supposed to be parentally determined. In
 136 addition, the expression of each gene j can be potentially modulated by an environmental factor E_j ,
 137 which can either upregulate ($0 \leq E_j \leq 1$) or downregulate it ($-1 \leq E_j \leq 0$). The environmental effects of all
 138 these N_e environmental factors ($N_e = N_g$), are contained within the vector E .

139 Developmental dynamics are attained by changes in gene concentration over a number of
 140 developmental iterations (t_{dev}), and the phenotype is recorded as the steady-state expression levels of

141 two arbitrarily chosen genes in t_{dev} (Fig. 1A). Only viable (temporally stable) phenotypes are
 142 considered: from 1 to N_g , the normalized G (represented here as G^*), must remain the same within a
 143 threshold of 10^{-2} over an interval of $t_{dev}/10$ developmental time units ($|G^*_{0.9 \cdot t_{dev}} - G^*_{t_{dev}}| \leq 10^{-2}$). The
 144 gene-gene interactions within the GRN follow a non-linear, saturating Michaelis-Menten dynamics
 145 (a special type of Hill function), so that the concentration of the gene i changes over developmental
 146 time according to the following differential equation:

147

$$148 \quad \frac{\partial g_i}{\partial t} = \frac{R(h_i)}{K_M + R(h_i)} - \mu g_i + \xi \quad (1)$$

$$149 \quad \text{where } h_i = \sum_{j=1}^{N_g} M_{ij} B_{ij} g_j + E_j \quad (2)$$

150

151 and $R(h_i)$ is the Ramp function ($R(x)=x, \forall x \geq 0$ and 0 otherwise) which prevents negative
 152 concentrations in gene products resulting from inhibiting genetic or environmental interactions. K_M
 153 is the Michaelis-Menten coefficient. Without loss of generality, we set $K_M=1$ (other choices of K_M or
 154 specific Hill functions are known not to affect the results, see [30]). The environmental term E_j is
 155 embedded within the gene-ordered summation of Eq. (2) following the associative property of the
 156 sum, and because $N_e \leq N_g$ always. Notice that, while environmental factors can effectively inhibit
 157 gene expression (if $E_j < 0$), they cannot turn a genetic concentration into a negative value (because of
 158 the Ramp function R). All genes and gene products (but not environmental factors) are degraded
 159 with a decay term $\mu=0.1$. In order to avoid unstable solutions, a certain amount of (Gaussian) noise
 160 is introduced in the system through the term ξ , randomly drawn from a Normal distribution $\sim N(0,$
 161 $10^{-2})$.

162 **-GRN + Multilinear model.** This model (based on [21]), can be viewed as a multi-linear model of
 163 phenotypic determination [20] that is added to a basic GRN-model [29] (Fig. 1B). The key difference
 164 with the previous model lies in how each phenotypic trait is generated. Rather than being the
 165 expression level of one element of the GRN, each trait $T_i, i=(1,2)$ receives a contribution from each
 166 transcription factor according to a linear coefficient:

167

$$168 \quad T_i = \sum_{j=1}^{N_g} Z_{ij} g_j \quad (3)$$

169

170 where the factor Z_{ij} represents the contribution of the j^{th} gene to the i^{th} trait ($-1 < Z_{ij} < 1$). Note that the
 171 Z matrix encoding the linear coefficients is separated from the matrix B encoding the GRN itself. In

172 this paper, the evolutionary implications of the correlations between maps are reported on the basis
173 of this model.

174 **-Lattice model.** This reaction-diffusion model (based on [30,31]) represents a simple
175 developmental model that implements multicellular phenotypes in an explicitly spatial context (Fig.
176 1C). The model describes on a one-dimensional row of N_c non-motile cells ($N_c=16$ in our case),
177 whose developmental dynamics is determined by a GRN (as described in the basic model) that is
178 identical for all cells. Interaction between the different cells is achieved through cell-cell signalling
179 involving extracellular diffusion of morphogens ($N_g/3$ of the GRN elements are considered to be
180 diffusible morphogens). Each of these morphogens has a specific diffusion rate D_i ($0 < D_i < 1$) and
181 follows Fick's second law. Zero-flux boundary conditions are used. Thus, the concentration of gene
182 i over developmental time now is calculated as:

183

$$184 \quad \frac{\partial g_{ij}}{\partial t} = \frac{R(h_{ij})}{K_M + R(h_{ij})} - \mu g_{ij} + \xi + D_i \nabla^2 g_{ij} \quad (4)$$

185

186 In most works that use this model, the phenotype is conceptualised as the expression pattern of one
187 of the constituent genes along the row of cells (e.g. [30,31]). Here, for the sake of comparability
188 with the other models used, we set T_1 and T_2 as the average concentration of gene 1 in the first and
189 last two cells of the organism ($T_1 = (g_{1,1} + g_{1,2})/2$, and $T_2 = (g_{1,N_c-1} + g_{1,N_c})/2$).

190 While these models differ in complexity, all three feature a GRN at their core, which is
191 defined by three types of variables – namely, regulatory connections, initial gene expression and
192 exogenous inputs (see Methods and Fig. 1). Together, these variables define the GRN dynamics
193 which, when implemented and iterated in the models, result in measurable phenotypes.
194 Furthermore, these three types of variables have some correspondence with the three types of
195 variation we address (genetic, parental and environmental). For example, parental effects generally
196 apply modification only in early stages, and thus can be allied to the initial gene expression values
197 of the GRN. This provides an intuitive way to link each of the constituent elements of the GRN to a
198 different source of phenotypic variation: (i) changes in gene-gene interaction strengths in the GRN
199 can be conceptualised as an effect of genetic variation; (ii) changes in the environmentally sensitive
200 elements in the GRN (sensor nodes and diffusion rates) as an effect of environmental variation; and
201 (iii) changes in the initial concentration of each transcription factor in the GRN as an inherited
202 initial state (Fig. 1D-F).

203 However, it is also true that, for example, an environmental input might change a regulatory
204 sensitivity and a genetic mutation might change an initial gene expression level, rendering the
205 correspondence non-univocal. This loose correspondence should be kept in mind in interpreting our

206 results, but we will show that the type of model variable itself entails a marginal explanatory power
207 when compared with other factors (i.e. the timescale of the change in these variables, see next
208 sections). In addition, even when the correspondence is not strictly one-to-one, our approach
209 exhausts the ways in which a specific GRN can vary (these variations do not alter the GRN
210 topology, which here is assumed to evolve much slower than the inputs [4,8]).

211 While more complex models (e.g. cell-based models including morphogenesis) could
212 implement environmental or parental inputs in the developmental dynamics in more ways than we
213 consider here (e.g. by changing the bio-physical properties of cells and tissues), the size of their
214 parameter spaces and their associate computational costs would render our approach unfeasible.
215 Notwithstanding this limitation of our work, comparing the results for these three different models
216 allows us to assess how the robustness of our results escalates with model complexity (see Fig. S2).

217 With the described settings, all the models used in this paper produce a single, 2-trait (2-
218 dimensional) phenotype for each combination of inputs. Thus, a set of phenotypes (i.e. a phenotype
219 distribution) can be generated by introducing variation in those inputs. These phenotype
220 distributions represented in a 2D morphospace are considered maps: those resulting from variation
221 in the genetic inputs are GP maps, whereas those resulting from environmental perturbations or
222 perturbations in the initial conditions are considered as EP and PP maps, respectively. While for
223 some authors (e.g. [31,32]) any map exhibiting phenotypic variation in response to genetic
224 mutations has the property of being evolvable; we consider a GP map to exhibit more or less
225 *genetic evolvability* to the extent that its phenotypic distributions are aligned with the adaptive
226 demands (in this sense, evolvability is a joint property of variation + selective environment, not a
227 property of the map alone; [9,10]). If a similar alignment is found in the EP map or the PP map,
228 they are said to exhibit adaptive plasticity and adaptive parental effects, respectively.

229 Considered together, the three maps encompass the whole set of phenotypes that a given
230 developmental mechanism can generate from the sum of all perturbations. This “total” variation,
231 which can be also represented in a 2D trait space, is referred to as a general phenotype distribution,
232 or GPD (i.e., the GP, EP and PP maps are all contained within this GPD, Fig. S1).

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Fig. 1. Experimental overview. Conceptual depiction of the three GRN-based models used in this work: (A) A pure GRN model where the (two-trait) phenotype is the steady-state concentration of two arbitrary genes. (B) GRN + Multilinear model, where each phenotypic trait is calculated as the weighted sum of all the elements within the steady-state GRN. (C) Lattice model, where the phenotype is conceptualised as the steady-state expression pattern of one of the constituent genes (Gen 5 in this example) along a one-dimensional row of cells that can communicate between them through cell-cell signalling. In all of these models, phenotypic variation is created by perturbing one or several elements in the core GRN: Perturbations can be introduced in the strength of gene-gene interaction (i.e. as genetic mutations, D); in some environmental cue may regulate some environmentally-sensitive gene (E); or in the (maternally inherited) initial concentrations of each GRN element (F). Perturbations on each of these three different sources of phenotypic variation (one element of the GRN perturbed at a time) will produce a collection of two-trait phenotypes (i.e., hind- and fore-limb lengths). If these phenotypes are plotted in a two-trait (T_1 - T_2) morphospace, they can reveal the structure of the parameter-to-phenotype maps (D-F, right panels). The linear slopes of these maps can be used as a coarse description of these maps, allowing for map-to-map comparisons of random (Fig. 2) and evolved GRNs (Figs 3-5).

GP, EP and PP mappings are correlated in randomly generated GRNs. We first explore the inter-dependence between GP, EP, and PP maps in a large ($n > 10^6$) ensemble of randomly generated GRNs (encompassing different GRN connectivities, topologies and number of genes, see Methods). We then separately introduced random variation (10 input values $0 < x < 1$) in the genetic, environmental and parental inputs (i.e., connection weights, expression levels, and initial conditions, respectively) of each of these GRNs, and compared the resulting phenotypic distributions, that is, the resulting GP, EP and PP maps.

We estimated the similarity between these three maps by testing whether or not variation in the genetic, environmental or parental inputs produce similar covariation between the two traits (Fig. 1D-F), using the linear slopes in the phenotypic morphospace as basic descriptors of the

264 different maps. Since comparisons were performed using the (linear, unordered) map slopes, and
 265 not the whole phenotypic distributions of each map, we used a simple (Pearson) product moment
 266 correlation to evaluate whether or not the slope of a map was associated with a similar slope in the
 267 other maps. Pairwise comparisons between the slopes caused by variation in genetic,
 268 environmental, or parental inputs were all significantly positive (Pearson $r \geq 0.3$; Fig. 2A). This
 269 demonstrates that GP, EP and PP mappings are not independent in random GRNs. Note that this
 270 positive correlation between maps does not imply that the map-specific slopes themselves are
 271 positive; only that their slopes, which can be positive or negative, are similar (a comparison
 272 between maps that does not consider the direction of the slope since genetic evolvability is
 273 concerned with the sensitivity to random mutations, not their direction; [9]). GRNs showing zero or
 274 negative correlation between different mappings also exist, but they are less frequent (Fig. 2B).
 275 Importantly, this interdependence across different mappings is robust to more detailed measures of
 276 map-to-map similarity, such as Euclidean distances (ED, Fig. S3). Such ED-based correlations,
 277 however, decrease as the difference between the map slopes become too large (presumably as an
 278 effect of map complexity itself, since complex maps are more dissimilar than simpler ones, see next
 279 section, Fig 2C, Fig. S3).

299 **Fig. 2. Phenotypic distributions arising from genetic, epigenetic or environmental perturbations are not independent.** In a
300 large random ensemble of GRNs ($n=10^6$), systematic parametric variations were introduced into each of their elements. Each
301 perturbation on an element generates a collection of phenotypes in a two-trait morphospace (a *XPM* map), characterised by a linear
302 slope S_{XPM} (see Fig. 1D-F). **(A)** For each GRN, we compare these slopes, two by two, searching for their correlations in the two-slope
303 spaces (note that these are not two-trait morphospaces). Each dot is a GRN, and the yellow shaded region contains 90% of the GRNs.
304 Correlations are significant (Pearson $r>0.3$) for every combination of maps considered. **(B)** Histograms showing the probability
305 distribution of maps with developmental insensitivity to the first ($S_x \leq 0.01$; yellow) or second ($S_y \leq 0.01$; red) type of inputs; and of
306 correlated (parallel slopes); anti-correlated (perpendicular slopes) and non-correlated slopes (otherwise). Each of these cases
307 correspond to the sector of a hypothetical circumference engulfing all points of (A), as exemplified in the coloured circumference,
308 and the relative frequency represents the probability of each point to be located within each sector. **(C)** The complexities of the
309 parameter-to-phenotype maps (i.e., how non-linear they are, see Methods); rather than between their linear slopes are also positive
310 (Pearson $r>0.56$). In (C), the colour represents slope similarity: similar slopes (black colour) are associated to simpler (i.e., more
311 linear) maps. $n=30$ replicates, GRN + multilinear model (see Fig S2 for correlations under other models and Fig. S5 for a null model
312 on C).

313
314 To eliminate the possibility that these observed correlations were caused by similarities in
315 the input values, rather than in the structure of the GRNs, we gradually randomized the input
316 parametric values while recording the correlations between maps (Fig. S4). This procedure revealed
317 that the correlations do not depend on particular choices of the input parameters. In contrast,
318 correlations were extremely sensitive to parametric changes in the GRN topology, suggesting that
319 the observed similarity between maps is caused by the structure of the GRN connections (i.e.,
320 ‘developmental mechanism’ *sensu* [30-32]) rather than the structure of the input perturbations.
321 While a relationship between specific GRN topologies and the strength of the map-to-map
322 correlations is expected (as it occurs for individual maps [30,31]), further studies would be required
323 to establish this relationship in more detail.

324 Another alternative explanation for our results would be that the observed correlations are
325 driven by the (close-to-zero) linear slopes associated with very complex (i.e. a “zigzag”-like) maps.
326 However, Fig 1A shows that even the central region of the correlational space where most ($>90\%$)
327 maps are contained shows a clear diagonal structure densely populated with non-zero ($1 < |S_x| < 2$)
328 slopes. Furthermore, if this would be the case, one would expect Euclidean distances between maps
329 to be generally very large (i.e. because most of them would be very complex and highly dissimilar
330 maps having both close-to-zero slopes). This possibility is rejected by our observations (Fig S3B),
331 which show that the majority of map-to-map Euclidean distances occurs at quite low values
332 ($ED_{A,B} \approx 2$), and is mostly constituted by relatively simple, sub-linear maps).

333 Finally, our simulations reveal that map-to-map correlations are affected in non-trivial ways
334 by certain GRN features, such as GRN size, connectivity, the number of iterations in the GRN
335 dynamics or the model architecture (Fig. S2). In general, correlations decrease as connectivity and
336 GRN size increase (presumably because large networks offer more opportunities for modularity,
337 which in turn may enable a developmental de-coupling between different traits).

338 **The complexity of GP, EP and PP maps are correlated in randomly generated GRNs.** We also
339 investigated whether or not the GP, EP and PP maps exhibit similar complexity in random GRNs.
340 We defined map complexity as the degree of non-linearity in phenotypic response to inputs. This
341 captures the intuition that a linear slope is less complex than a U-shaped response, which is itself
342 simpler than a W-shaped response. Comparing the map complexities between the 10^6 random GRNs
343 reveals that map complexities are, on average, positively correlated (Pearson $r \geq 0.56$; Fig. 2C and
344 S2). In other words, if a map (e.g., GP) is simple, the other maps (EP and PP) will be simple too,
345 and they will exhibit very similar slopes. In contrast, if a map is complex, other maps too are likely
346 to be complex, and their slopes will be less similar (Figs. 2C and S2).

347 To ensure that these observed correlations between map complexities are not a general
348 property of pairs of input-output maps, we analysed a large ensemble of random mathematical
349 functions (polynomials of known degree ≤ 4) using the same tools that we used for calculating map
350 complexity. This analysis verified that the correlations do not arise between pairs of randomly
351 selected functions unless they belong to the same complexity class (polynomial degree) (Fig. S5).

352 How a network topology creates similarity between map slopes and complexities can be
353 better understood by looking at the whole set of developmentally attainable phenotypes (general
354 phenotypic distribution: GPD), which can be revealed by means of massive and unspecific
355 parametric perturbations (see Methods and Fig. S1). This procedure shows that each generative
356 network creates a distinctive GPD with a highly anisotropic and discontinuous structure. This
357 structure increases the likelihood that individual maps will have similar slopes simply because
358 many phenotypic directions of change are either very unlikely or developmentally impossible (Figs.
359 S1, S2, S4 and S5).

360 Positive map-to-map correlations in both slopes and map complexities were found in all
361 three considered models of phenotypic determination (Fig. S2). However, the correlation
362 coefficients are higher and more variable for complex models involving more than pure-GRN
363 dynamics (Figs. 1B-C and S2).

364

365 **Evolving only one of the GP, EP or PP maps changes the phenotypic biases across the other**
366 **maps.** After exploring the map-to-map correlations in random GRNs, we next wanted to address
367 whether or not adaptive changes within one map (i.e., changes in the covariation between traits) are
368 able to induce similar changes to the other maps. To do so, we performed three sets of selection
369 simulations using the developmental model of intermediate complexity (GRN + multilinear). This
370 model was chosen because it is the one showing more stable map-to-map correlations under a wider
371 range of assumptions and GRN properties (see Fig. S2). In each simulation, we allowed only one of

372 the three different maps (henceforth the “selected map”) to evolve in response to selection. We refer
373 to the other maps as the “non-selected” maps (see Methods for details).

374 Although an individual may experience many environmental inputs during its lifetime, it has
375 only one genotype and, generally, one parental input (here initial condition). This means that, in one
376 generation, natural selection can act on a distribution of environmentally induced phenotypes, but
377 only on a single phenotype produced by genetic variation (that is why the evolution of GP and PP
378 maps would ordinarily require lineage selection over many generations). Our main point in this
379 paper depends, indeed, on the fact that this difference in the selective timescale makes selection for
380 phenotypic plasticity likely to be a strong driver of genetic evolvability, but not vice versa (see next
381 sections). But, before we get to that, it is necessary to first examine how evolving one map
382 influences other maps, and to examine this properly it is necessary to be able to apply an equally
383 effective, fine-grained selection on each of the selected maps. While introducing similar rates of
384 change in the genetic, environmental and parental inputs is biologically unrealistic, it enables us to
385 examine the evolutionary interdependence of the maps that arise because of their developmental
386 linkage, while removing the differences in their capacity to be selected (next experiments will
387 address more biologically grounded cases).

388 To adaptively evolve the “selected map”, an initial heterogeneous population of $p=64$
389 individuals is composed by randomly picking each individual (GRN) from the initial random
390 ensemble. According to our previous experiments, each of these individuals exhibits certain “by
391 default” correlation between its maps, yet the average slope of the maps at population level show no
392 particular direction (Fig. 3A). At each evolutionary time step (i.e. within a generation time and for
393 each individual in the population), we introduce variation only in the input associated with the
394 selected map (i.e., genetic, environmental or parental inputs). To make comparisons possible, only
395 one element (e.g. one gene) is varied at a time for each type of input.

396 In response to the variation on one type of input, each individual develops a set of
397 phenotypes that is compared to an arbitrary (linear) target map to determine the individual’s fitness.
398 In turn, the individual’s fitness determines the likelihood of that individual to contribute to the next
399 generation. Thus, the entire phenotype distribution produced by the selected map is accessible to
400 natural selection (i.e., fine-grained selection). In contrast, the inputs of the non-selected maps were
401 kept fixed (no variation) during simulations, so that these maps remain effectively “invisible” to
402 natural selection (Fig. 3A). Notice that this selection criterion does not select for particular
403 phenotypes, but for particular biases (i.e. trait correlations) in the maps themselves. This procedure
404 allows us to accelerate the weak selection on variation that is found on natural populations, where it
405 is performed indirectly through individual-level selection of phenotypes [9,10,33,34].

406 In each generation, a number of random point mutations are introduced in the GRN
407 parameters and in the multi-linear coefficients (as in [21], see Methods) of the new individuals.
408 Such changes in the developmental architecture may change the way in which organisms respond to
409 the focal inputs, thus creating new selectable variation in the slope of the selected map, and
410 allowing adaptive change in the long-term (<1000 generations). Once each evolutionary simulation
411 reached a steady state, we assessed if there were any changes in the non-selected maps. We did this
412 by: 1) introducing variation to each of the non-selected maps (one by one), and 2) collapsing the
413 variation for the selected map to a single input value $x \sim U(0,1)$. In the “collapsed” maps, we
414 deliberately avoid setting $x=0$ to ensure that our results are due to the lack of variation in the inputs
415 and not to the absence the input itself.

416 That is, if the selectable phenotypic distribution had been originated exclusively through
417 variation ($0 < x < 1$) in the parameters of type “A” (e.g. genetic), and keeping the all parameters of B
418 (e.g. environmental) and C (e.g. parental) types fixed; now all “A”-type parameters are kept fixed
419 and parametric variation is introduced, alternatively, in the “B”-type and “C”-type parameters to
420 quantify the newly arising phenotypic distributions (see Methods). This experimental setup
421 guarantees that any observed changes in non-selected maps can be attributed to indirect effects of
422 selection on the selected map.

423 The results revealed that evolving any one map modifies the other maps as well, introducing
424 in them the same adaptive phenotypic biases as observed in the selected map (Pearson $r > 0.3$, Fig.
425 3A). This holds true for every map combination (Fig. 3B) and across the entire range of parameters
426 we tested (Fig. S2). However, the phenotype biases in the non-selected maps are not as strong ($|r|$
427 < 0.5 in some cases) as in the map under selection ($r = 0.99$), and exhibit substantial temporal
428 variation, with non-selected maps lagging behind the selected map (Fig. 4). The results in Figure 3
429 illustrate the outcome of selecting for a linear map with a slope $S = 1$ in the two-trait morphospace,
430 but simulations with $S = -1$ or with changing selective pressures yielded similar results (Figs. 4, S6).

431

432

Fig. 3. Evolving a single map creates similar phenotypic distributions in the other maps. A population whose individuals initially exhibit a random phenotypic distribution in $t=0$ (A, small panels) is evolved to fit a target phenotypic distribution ($S^T=1$) using as an input just one kind of phenotypic determinant (i.e., genetic, environmental, or parental variation). Other targets ($S^T=-1$) give similar results (see Fig. S6). In each generation, one individual is exposed to 10 different input values ($0 < x < 1$) of a single phenotypic determinant (the colour of each dot in A-B represents value of this input). This parametric variation produces a set of ten potential phenotypes whose slope is compared to the target to evaluate the individual's fitness (see Methods). After 10^5 generations in a mutation-selection-drift scenario (where other sources of phenotypic variation are frozen), the population has a narrow phenotypic distribution in the evolved map (A, large panels). In (B) we uncover variation in the other maps by introducing parametric variation ($0 < x < 1$) in the phenotypic determinants that were kept fixed during the evolutionary trial. Results reveal that selection on a single map creates significant side-effect phenotypic distributions in the other maps that are not the target of selection. (C) Correlations in the side-effect maps are significant across all parameter values at which the parameter of the evolved map is frozen. $p=64$ individuals; $n=30$ replicates, GRN + Multilinear model.

Maps evolve faster under fine-grained selection than under coarse-grained selection. In the previous experiments, each evolving population was allowed to sample a wide range of genetic, parental or environmental inputs in each generation, and selection therefore acted on a wide range of phenotypic outputs. In other words, we assumed a very fine-grained selection. This allowed us to see how adaptation in each individual map would affect the other maps in the hypothetical case where selection is able to effect change in the selected map easily. In natural populations, such fine-grained selection cannot be assumed, so in this section we examine the effects of relaxing this simplifying assumption. To that end, the previous results under idealized, very fine-grained selective scenarios are taken as a “null hypothesis”, and compared against more coarse-grained regimes.

Several studies show that adaptive plasticity readily evolves when selection is fine-grained [35-37], although it is not essential [33]. Whether or not a similar effect occurs for GP and PP mappings is unknown. To address this, we explored the ability of every map to adapt to a target map under different levels of selective grain, ranging from very fine-grained selection (where individuals can experience several inputs within their lifetime) to coarse-grained cases in which there is just one input per generation and this input only shifts every n generations.

Fig. 4. Side-effect phenotypic distributions are able to track shifting targets. These plots show how initially unstructured populations are able to adaptively evolve a specific target distribution (a single map with a defined slope of $S^T=1$, solid lines), which creates as a side-effect correlated phenotype distributions in the other maps (dashed lines). Notice that evolutionary time is plotted here in a Log_{10} scale, so that adaptation to the target maps occurs actually very fast (i.e. in a few generations). The middle point corresponds to the steady-state situation shown in Fig. 3. For these plots, the target slope has been shifted to $S^T=-1$ at generation $t \sim 10^4$, showing how the maps that evolve as a side-effect are able to “follow” the one that is being selected. This pattern is similar for every map considered. $p=64$ individuals; fine-grained selection (identical selective grain for each map); $n=30$ replicates, GRN + Multilinear model.

As Fig. 5 shows, all maps are in principle equally responsive to strong selection, yet all of them evolve more efficiently under fine-grained selection than under coarse-grained selection. Furthermore, the ability to adapt to the target map escalates sharply around a grain value of 1 (Figs. 5 and S8). Under the metrics adopted here (see Methods), this is the value where single individuals experience on average more than one input per generation. This implies that it is much easier to evolve a map efficiently, and thus to affect the other maps, if there is within-lifetime variation in the inputs to that map. This disproportionate effect of the most fine-grained screened map on adaptive evolution is observed even when all the three maps are simultaneously selected (Fig. S7).

Besides selective grain, the ability of GRNs to evolve a target map also depends on the complexity of the target map (i.e., how non-linear is the phenotypic response to input variation). Simple (i.e., linear) maps can easily evolve with moderate fine-grained selection (≈ 2 inputs per lifetime) whilst evolving more complex (i.e., quadratic or cubic) map requires an increasing number of inputs per lifetime (Fig. S8).

While universal differences in complexity between maps are hard to conceive of (examples of simple and complex responses have been reported for GP, EP and PP maps), there is a clear, widespread difference in the selective grain of the three maps. This arises from the fact that, in most organisms, individuals can experience different environmental inputs during their lifetime but are limited to a single genotype and a single set of parentally inherited initial conditions. As a result, the EP map selection would be most fine-grained, and hence the one most intensely sculpted by natural selection. Because of this asymmetry, the EP map can exercise a stronger influence on the other maps than *vice versa* (Figs. 5 and S7). In other words, while every map can *theoretically* be the leader of adaptive evolution, the logic by which natural selection operates in real-world organisms makes the EP map a prominent driver of evolutionary dynamics. The generality and the evolutionary consequences of this are further discussed in the next section.

Fig. 5. Map evolvability depends on selective grain, and it is maximal for Environment-Phenotype maps. In Figs. 3 and 4, simulations assumed that natural selection could act on the entire map. Since we define selective grain as the average number of parameter-phenotype points that be experienced by a single individual in each generation (and hence “seen” by natural selection, see Methods), this corresponds to very fine-grained selection. In this experiment, the assumption about high fine-grainedness has been relaxed. For each level of selective grain, the ability of natural selection to evolve a linear map with an arbitrary slope is recorded as the Euclidean-distance (ED)-based fitness after $t=10^4$ generations. Points correspond to individual replicates, and dashed lines to averages over the $n=30$ replicates. Point colour represents map type. For each replicate, the target map is a linear function of arbitrary non-zero slope. These plots show that the ability to adapt to a target slope increases non-linearly with selective grain, and that maximal efficiency is achieved when selection is fine-grained (>1), which corresponds to scenarios in which single individuals can experience more than one input per generation. Such high levels of selective grain are typically only attainable for Environment-Phenotype (EP) maps (see main text). In the GP and PP-maps, in contrast, such high levels of fine-grainedness (inputs/generation >1 ; greyish shadowed areas) represent biologically unrealistic scenarios that can only be revealed by means of *in silico* experiments. However, understanding the evolutionary dynamics in these “unbiological” regions is fundamental to establish whether the evolutionary dynamics observed in real-world populations arise from differences in the selection grain between maps or from other confounding factor(s) (see main text for a discussion). $p=64$ individuals, GRN + Multilinear model.

Discussion

Understanding how the processes that generate phenotypic variation interact with natural selection is necessary to explain and predict the course of evolution [3,5,7,38]. While it is easy to understand that any developmental bias aligned with adaptive demands would facilitate adaptation, it is not obvious how these biases originate, nor how they might change or be maintained over evolutionary time. Phenotypic adaptation can precede genetic adaptation, and it has been suggested that plasticity therefore facilitates genetic evolution (reviewed in [23]). However, trying to explain genetic evolvability (i.e., adaptive phenotype biases in response to random mutation) by presupposing the existence of adaptive plasticity overlooks the fact that adaptive plasticity is itself a product of genetic evolution. If explaining adaptive plasticity requires past genetic evolution to have already produced adaptive phenotypic responses to particular environmental cues, this does not help to explain genetic evolvability itself. The idea that plasticity and evolvability are intrinsically linked through development provides a way that selection for plasticity can result in the evolution of genetic evolvability, as studied here. Our aims have been to explore this linkage using mechanistic models of developmental dynamics and thus explore the evolutionary consequences of the relationship between plasticity and evolvability.

Our results show that a concordance between the GP, EP and PP maps is intrinsic to developmental dynamics based on GRNs (with or without selection). Because of this concordance, selection for any map will affect the other maps in an essentially symmetric fashion. However, the efficacy of natural selection in sculpting the different maps is not symmetric because selection for the EP map can be much more fine-grained than selection for the genetic evolvability. Accordingly,

574 selection for plasticity can be much more effective in changing the GRN and genetic evolvability
575 than direct selection for genetic evolvability. Thus, without overlooking the fact that adaptive
576 plasticity is itself a product of genetic evolution, we show how the genotype-phenotype (GP) map
577 can be adaptively shaped by selection for phenotypic plasticity, suggesting that adaptation to
578 environmental variation helps explain the remarkable genetic evolvability of organisms in nature.
579 This finding complements the previous notion that selecting for plasticity may increase the amount
580 of (raw) genetically induced phenotypic variation [21]: we show now that such new induced
581 variation is not only larger but, *in addition*, preferentially aligned with the direction of the adaptive
582 plastic responses.

583 The results show that the phenotypic effects of genetic and environmental sources of
584 variation are typically similar across a wide range of assumptions. This finding is in agreement with
585 previous research that found similar correlations on other theoretical grounds or for more restricted
586 scenarios, such as selection for developmental robustness to environmental perturbation [16-
587 19,21,24]. In a general sense, all these results suggest that organisms exhibiting adaptive plasticity
588 will be expected to have high genetic evolvability, and *vice versa*. However, the inclusion of the
589 parental (PP) map in our analysis allows us to further generalise our results, suggesting that, by
590 virtue of a shared developmental dynamics, most parametric perturbations in a developmental
591 system will “map” to a similar set of phenotypes. Moreover, since the concordance appears in
592 randomly generated regulation networks, it does not require the concurrence of past selection to
593 produce this concordance. Rather, stability analysis revealed that correlations between GP, EP, and
594 PP maps are caused by the structure of the network itself and its associated dynamical properties.
595 Although this result might be expected for statistical models that assume linearity and additivity
596 (e.g., the equality $P=G \times E$ from quantitative genetics, [39]), it is non-trivial for mechanistic models
597 like the ones presented here since these involve non-linear interactions between the inputs. These
598 interactions create a non-uniform space of phenotypic possibilities (a generalised phenotype
599 distribution; GPD) that includes regions of the morphospace that most of the parameter
600 combinations map onto (i.e., phenotypic attractors; [18,32]), and ‘forbidden’ regions that cannot be
601 attained by any parameter combination. This does not imply that the GPD has an exaggerated
602 robustness preventing the existence of ample phenotypic variation. Rather, these features of the
603 GPD impose strong limitations on the phenotypic variation that is possible, and the shape of the
604 genotype-, environment-, and parental-phenotype maps will be similar since they share the same
605 attractors (i.e. they must be contained within the same variational structure, Fig. S1). Such complex
606 attractors are an inherent property of many dynamical systems, and can be only revealed by means
607 of mechanistic models or advanced mathematical tools [4,7,31,32].

608 The reduced degrees of freedom of these shared attractors explain why a population that has
609 evolved a specific (e.g., EP) map will show similar biases in all its maps, even when those have not
610 been selected for. However, this dependence would not make plasticity exercise a disproportionate
611 effect on genetic evolvability unless there was some asymmetry that makes selection for properties
612 of the EP map more efficient than selection for properties of the GP or PP maps. We show that this
613 crucial asymmetry follows from differences in the temporal timescale ('grain') of environmental,
614 parental and genetic variation that is input to these maps. Specifically, the variational properties of a
615 map evolve faster when individuals experience multiple inputs, and hence can develop multiple
616 selectable phenotypes, during their lifetime [35-37]. While individuals can experience multiple
617 environments during their lifetime, they do not experience multiple genotypes or initial conditions
618 (e.g., the distribution of phenotypes produced under genetic variation is a property of a family,
619 population or lineage, not an individual). As a result, selection for GP and PP maps should typically
620 be more coarse-grained and less efficient than for EP maps. This general property of natural
621 selection suggests that adaptive EP maps will generally evolve more readily than adaptive GP (and
622 PP) maps, even though they depend on the same developmental dynamics. Notice that the reverse
623 situation (plasticity lagging behind the other maps) might be also possible in some special cases of
624 long-term environmental stasis (e.g., abyssal or deep-soil communities) but, in most evolutionary
625 scenarios, the evolution of phenotypic plasticity would lead the evolution of genetic evolvability
626 much more easily than *vice versa*.

627 These results generate predictions that can be tested empirically, for example, by means of
628 experimental evolution. One particularly useful approach would be to select populations in
629 environments of different variability (i.e., selective grain), which should result in populations with
630 different EP maps. The prediction is that the finer the selective grain, the more the structure of the
631 GP map will resemble that of the EP map, which can be tested using mutation accumulation
632 experiments or genetic engineering. Whether or not such changes in the GP map changes the
633 capacity for future adaptation could be tested by exposing populations to new selective regimes that
634 are more or less structurally similar to those that the population was initially adapted to. Other
635 experimental and comparative approaches could also test one or several of the predictions of the
636 relationship between EP, PP, and GP maps (e.g., [12,19,40,41]).

637 While our results demonstrate that natural selection on phenotypic plasticity would cause the
638 GP map to evolve, they also show that the ability to evolve a certain map is severely limited by the
639 map complexity itself, with complex (e.g., cubic) maps requiring highly fine-grained selection. This
640 would render very complex EP (and GP) maps unreachable by adaptive evolution even in the most
641 fine-grained scenarios [34]. However, complex maps are known to exist, which suggests that other
642 non-selective processes, such as developmental system drift [31,42], may play an important role in

developmental evolution [3,38]. This possibility is compatible with our results, which simply state that whenever adaptive developmental biases do exist, they will be predominantly the result of past selection for phenotypic plasticity. Furthermore, since each trait needs to maintain its function as other parts of the organism develop and grow, selection for plasticity can be even more fine-grained than expected (our models do not fully capture this developmental dependence because they record the individual fitness after a fixed developmental time).

These results shed light on whether or not plasticity can exercise a predominant role in adaptive evolution, a hypothesis with a long and contentious history in evolutionary biology [13,21-23,43,44,45]. While adaptive modification of environmentally induced phenotypes can make plasticity appear to ‘take the lead’ in evolution without any link between plasticity and genetic evolvability [13,41], the evolutionary change in the GP map caused by adaptive plasticity suggests that evolution is particularly likely to proceed where plasticity leads. Over longer timescales, this process provides a biologically plausible mechanism for the internalisation of environmental information, resulting in developmental biases whose structure ‘mirrors’ the structure of the selective environment [46], and thereby facilitating further adaptations through genetic modification of environmentally induced phenotypes [8,13,21,33]. Without denying the importance of other (adaptive and non-adaptive) processes (e.g. [42]), this constitutes a strong argument for a role of plasticity in shaping the path of evolution.

Note that our results do not imply that phenotypic plasticity is a leader in the sense that it arises without genetic evolution. Rather, we suggest that the *genetic evolution of* plasticity comes first, and this causes (by common cause of developmental mechanics) the evolution of genetic evolvability along the phenotypic directions that were initially plastic. This account is fully compatible with natural selection on genetic variation as a prime-mover in evolution and yet suggests a meaningful sense in which phenotypic plasticity comes before genetic evolvability.

Conclusions:

In summary, our work reports a previously ignored process that explains how development can turn random genetic variation into adaptive phenotypic variation. Such process, which entails an enhanced scope for adaptive evolution, emerges naturally from a combination of two different and well established phenomena. The first is that development makes the phenotypic consequences of genetic and environmental changes generally similar. Therefore, selecting for particular responses to environmental variation (i.e., phenotypic plasticity) can affect the way organisms respond to genetic mutations (i.e., their genetic evolvability) and *vice versa*. The second is that natural selection is more efficient in evolving phenotypic plasticity than genetic evolvability

(making plasticity to be generally adaptive). The developmental linkage allows these adaptive responses to environmental variation to be transferred to the genotype-phenotype map, thereby facilitating the generation of adaptive phenotypic variation through genetic change. These findings suggest that organisms can evolve in the long term by exploiting changes to the G-P map that were originally evolved for their capacity to plastically adapt in the short term.

683

684 **Methods:**

685

686 Correlations between maps. A large ensemble ($n=10^6$) of random GRNs was created by setting the probability of non-null genetic interactions to $p(B_{ij} \neq 0) \sim U(0,1)$. In addition, we uniformly sampled the GRN space of networks between 3 and 24 genes, ($N_g \sim U(3,24)$) so that a variation in GRN size and connectivity were represented (by virtue of the central limit theorem, average GRN size and connectivity are, respectively, $N_g \approx 14.5$ and $p(B_{ij} \neq 0) \approx 0.5$). Environmental inputs were also assigned randomly, being each element of the G vector drawn from an exponential distribution $E_i \sim \text{Exp}(\lambda=1)$. This ensures that just some environmental inputs are able to interfere effectively with developmental dynamics (otherwise the effect of environment on GRN dynamics would be too large). The same ensemble was used for the three models. Model-specific elements were randomly drawn: $Z_{ij} \sim U(-1,1)$; $D_i \sim U(0,1)$. For each random GRN, parameter-to-phenotype maps were generated through systematic (parametric) perturbations in each of the GRN elements. The element perturbed was randomly chosen for each replicate ($n=30$) and given values from 0 to 1 at 0.1 intervals (in this work, the input values of the different maps are of similar magnitude, an idealisation that allows us to compare the evolutionary properties of the different maps). During these perturbations, GRN topology was always held fixed. Perturbations in B_{ij} were conceptualised as genetic changes; in G_0 as changes in the initial conditions (i.e., parental effects); and in E_j or D_i as environmental changes (Fig. 1). That way, the systematic perturbation of each element generated 10 different phenotypes that were recorded in a two trait morphospace, constituting a map (GP map, PP map or EP map, respectively). Note that our “maps” are not maps in a formal mathematical sense because they do not retain the univocal relationship between the inputs and the outputs. However, they allow us to compare different phenotypic distributions whose inputs have different units and magnitudes.

We focus on two-trait phenotypes because they embody the minimal multivariate system where associations between traits can be found. These maps were compared, two by two, using two measures of map-to-map similarity. The first is a coarse-grained measure: Pearson’s r correlation between the two linear slopes in the phenotypic morphospace (Fig. 2). In order to take into account negative and close-to-zero slopes, the original slope values were transformed to

713 $S_a = \text{sgn}(S) \cdot \text{Log}(1+S)$, so that negative values correspond to negative slopes, and not to $0 < S < 1$
 714 (therefore, the radially symmetric distribution of points around the origin (0,0) observed in in Fig.
 715 2A suggests that individual trait-trait correlations across maps have similar likelihood of being
 716 positive or negative). Two maps a and b were said to be correlated or uncorrelated depending on
 717 their sectorial position in this correlational (S_a, S_b) space: $\text{corr}(a, b) \leftrightarrow |\tan^{-1}(S_a/S_b) - \pi/4| \leq \pi/12$,
 718 $\text{anticorr}(a, b) \leftrightarrow |\tan^{-1}(S_a/S_b) + \pi/4| \leq \pi/12$, and not correlated otherwise (Fig. 2B). The second, fine-
 719 grained measure is the Euclidean distance ($ED_{a,b}$) between maps a and b (Fig. S3):

$$720 \quad ED_{a,b} = \sqrt{\sum_{j=1}^{10} (T_{aj1} - T_{bj1})^2 + (T_{aj2} - T_{bj2})^2} \quad (5)$$

722 where T_{ijk} is the value of trait k in the j^{th} phenotype of map i . As Fig. S3 shows (panel A), $ED_{a,b} \propto |S_a/S_b|$. As a proxy for map complexity (C_a) we use the sum of the squared residuals of each map with
 725 respect to its linear regression, which simply measures the quality of the fit of the map to the linear
 726 function $y = S_a \cdot x$; where S_a is the slope of the map itself. While more mathematically precise
 727 measures of map complexity can be envisioned (e.g. Bayesian Information Criteria, Fourier
 728 analysis), our measure intuitively captures the notion that the more a map departs from a perfect
 729 line the more complex it is:

$$730 \quad C_a = \sum_{i=1}^{10} (T_{i2} - T_{i1} S_a)^2 \quad (6)$$

732 where T_{ij} is the value of the trait j of the i th point (phenotype) of the map considered. For this
 733 analysis maps were re-scaled to $(0 < T_{ij} < 1)$ values in order to avoid size-effects on the map
 734 complexity (otherwise the squared residuals of maps with large phenotypic values would result in
 735 artefactually higher complexity) (Fig. S3B). We assess the effect on map-map similarity (slopes and
 736 map complexities) of GRN size (N_g) and connectivity $p(B_{ij} \neq 0)$ (Fig. S4), but not of GRN topology
 737 itself as this is beyond the scope of this work (for a discussion on this see [30,31]).

739
 740 **Numerical integration.** Following [30,31,38], all the differential equations (1 and 4) were
 741 numerically integrated using the Euler method ($\delta t = 10^{-3}$).

742
 743 **Control experiments.** Two control experiments were set up to better understand the causes of the
 744 observed correlations between slopes S and map complexities C . In the first, with a probability
 745 $p = \{0.1, 0.2, \dots, 1\}$, GRN topology was changed as $M_{ij} \rightarrow |M_{ij} - 1|$ and the GRN input values as
 746 $x \rightarrow x \sim U(0, 1)$. Then, correlations were recorded between the maps arising from the unperturbed

GRN (S and C) and the randomized ones (S^* and C^* , Fig. S4). In the second control experiment, we used a set of randomly generated mathematical functions (polynomials $f(x)$ with known degree $\deg(f) \leq 4$) as a null, non-generative space in which we could test whether the observed correlations between map complexities are a general property of any mathematical function rather than a biologically relevant phenomenon (argument and value of $f(x)$ are considered to correspond to the traits T_1 and T_2). A discrete “mapping” was created by assigning ten values to $x = \{0.1, 0.2, \dots, 1\}$, and then calculating the corresponding y -values (Fig. S5):

$$y(\approx T_2) = \sum_{i=0}^4 R_{(i)} x(\approx T_1)^i e^{-i} \quad (7)$$

where R is a vector of random numbers $R(i) \sim U(0,1)$ and e^{-i} a corrective token that devalues the high-degree terms of the function, ensuring that polynomials of different degrees are equally represented. If necessary, y -values were rescaled to $(0 < y < 1)$, as in Fig. S3), so that the map complexity of the the function was measured under the same conditions as for GRNs.

Evolving maps. Several of our experiments involve the adaptive evolution of a map: a population of $p (=64)$ haploid individuals picked from the random ensemble evolves in a mutation-selection-drift scenario until a map with a target slope S^T is encountered, or until a maximum number of $t_{max} = 10^5$ generations is reached (non-overlapping discrete generations are used in all simulations). Arbitrarily, S^T is set to $S^T = 1$ (other choices do not alter the results, see Fig. S6). With a rate of 0.04 ($\approx 1/N_{gmax}$) per element and generation, point mutations are introduced in the matrices encoding the topology and interaction strengths of the GRN: $B_{ij} \rightarrow B_{ij} + \xi$ ($\xi \sim N(\mu, \sigma)$; $\mu = 0$, $\sigma = 0.01$) and $M_{ij} \rightarrow |M_{ij} - 1|$. The same rate of change is applied to the coefficients of the multi-linear model used in the evolutionary simulations, which mutate as $Z_{ij} \rightarrow Z_{ij} + \xi$ ($\xi \sim N(\mu, \sigma)$; $\mu = 0$, $\sigma = 0.01$). Such a mutation process is applied to every individual within the population at every generation. The fitness of each individual W_i is calculated on the basis of its ability to create a map similar to the target one (not on the basis of a single phenotype). Thus, each individual in each generation is exposed to 10 different inputs in one of its GRN elements (the element depends on the map being evolved), and its slope S_i in a T_1 - T_2 morphospace recorded and compared to the target slope S^T . This algorithm is formally equivalent to an inter-generational variation in the inputs [33-35]. The similarity with the target slope determines the individual’s fitness and, in turn, the probability of each individual to contribute to the next generation:

$$W_i = e^{-|S_i - S^T|} \quad (8)$$

Some of our experiments involve different levels of selective grain on the maps, which has two different components: intra-generational (i.e., how many different inputs (or points of the whole map) can the population experience in a single generation) and inter-generational (i.e., how often these inputs change, which can be conveniently expressed as the number of generations between changes in the input values). For the sake of simplicity we collapse these two components in a single composite measure of fine-grainedness as inputs/generation (Figs 5, S7 and S8). Since slopes alone cannot account for the number of points in a map, the fitness is now calculated as:

$$W_i = e^{-ED_{map_i, map^T}} \quad (9)$$

where ED_{map_i, map^T} is the Euclidean distance, point by point, between the individual's map (map_i) and the target map (map^T), as described in Eq. (5).

Ethics approval and consent to participate. Consent for publication: Not applicable.

Competing interests: The authors have declared that no competing interests exist.

Funding: This work was funded by the Templeton Foundation (Grant 66501). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions: M.B.U., T.U. and R.A.W. conceived the idea, that was later refined by all the authors. M.B.U., A.R., Ch.T. and R.A.W. established the experimental design. M.B.U. wrote the software and conducted the in silico experiments. All authors equally contributed to the interpretation of the results. M.B.U., A.R. and R.A.W. drafted the manuscript, which was later refined and improved by M.B.U. and T.U.

Data availability: All relevant data are within the manuscript and its Supporting Information files.

Acknowledgements: The authors thank J.F. Nash, D. Prosser, J. Caldwell, L.E. Mears, R. Zimm and I. Hernando-Herraez and for helpful discussion and comments.

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