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Developmental autonomy and somatic niche construction promotes robust cell fate decisions

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ABSTRACT

During the course of development cells undergo division producing a variety of cell types. Proliferation and differentiation are dependent on both genetic programs, encoded by the cellular genome, and environmental cues produced by the local cellular environment imposing local selection pressures on cells. We explore the role that cellular signals play over a large range of potential parameter regimes, in minimizing developmental error: errors in differentiation where an inappropriate proportion of differentiated daughter cells are generated. We find that trophic factors produced by the population of dividing cells can compensate for increased error rates when signals act through a form of positive feedback—survival signals. We operationalize these signals as the somatic niche and refer to their production as somatic niche construction. We find that tissue development switches to an autonomous state, independent of cellular signals, when errors are unmanageably high or density regulation is very strong. A signal-selective regime—strong niche dependence—is favored at low to intermediate error, assuming compartmentalized density dependence.

1. Developmental programs and selective arenas

Development proceeds through a complex interplay of genetic programs and environmental signals. The extent to which differentiation depends on environmental cues varies according to both cell type and species-specific characteristics (Watt and Hogan, 2000; Varjosalo and Li, 2006; Dzierzak and Speck, 2008). Our goal is to explore conditions favoring either developmental autonomy or signal dependence, treated operationally throughout this paper as opposite strategies with respect to sensitivity to feedback (Reya and Clevers, 2005). Autonomous cells minimize their reliance on their local cellular environment, in particular their density-dependent sensitivity to signals produced by neighboring cells. Developmentally sensitive cells are associated with a strong density-dependent sensitivity to signals generated by the local somatic niche. In this case the niche provides local, developmental selection pressures.

Many cells, including those of the developing, freshwater coelenterates, those of leeches, and diverse forms of tumor cells, are virtually impermeable to outside signals (Zackson, 1984; Evan and Vousden, 2001). On the other hand, most mammalian tissues depend on external signals to provide information for the maintenance of homeostasis and adaptive responses to stress (Domen and Weissman, 1999).

We present a model for cell division and differentiation within an organism in order to characterize a variety of thresholds where it becomes advantageous for a lineage of cells to switch from an autonomous state, reliant largely on genetic or epigenetic programming, to a sensitive state where cells become more responsive to local environmental (cell derived) signals.

We define a healthy developmental trajectory as one that minimizes the difference between a putative, zero error trajectory for a tissue, and a noisy trajectory to include perturbations in terms of both developmental errors (deviations from the baseline distribution of cells) and dissipative errors (deviations from the baseline abundance of cells).

This approach to development is related to the ideas that Waddington pursued on developmental canalization (Waddington, 1959), seeking to account for low levels of phenotypic variance (deviation from a normal or functional target tissue or form) given high levels of genetic polymorphism for traits in a population. Waddington sought to explain the ability of organisms to withstand perturbations, both genetic and environmental, and remain capable of generating functional phenotypes.

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An extensive literature on robustness seeks to identify those mechanisms responsible for the canalization of development (Arjan et al., 2003).

Our approach also relates to an historically ongoing debate, centering on the role that selection processes during development play in generating functional phenotypes. Following the early work of Weissman (1903) and subsequent contributions by Buss (1987) and Klekowski (1988) on developmental selection, researchers have become increasingly aware of the critical role played by variation and selection within an individual during ontogeny. This research either emphasizes mechanisms generating variation, such as in the theory of facilitated variation (Kirschner and Gerhart, 1998), or those signals acting as local selection pressures within developmentally, competitive arenas (Stearns, 1987), in the theory of somatic selection (Krakauer and Pagel, 1996; Krakauer and Mira, 1999). These studies emphasize the crucial role of adaptive dynamics in generating functional variability and plasticity, and in compensating for developmental errors.

Through modeling we seek to reconcile Waddington's observations on the canalization of development, with population-based mechanisms of somatic selection within an organism mediated by cellular signals. Signals generated by a population of cells, capable of generating density-dependent selection pressure, are shown under a range of error rates to restore a desirable distribution of cell types within a tissue by homeostatically modifying proliferation and differentiation rates.

2. The embryonic selection arena

The process of embryogenesis exemplifies an organism's ability to coordinate concurrent differentiation pathways so as to minimize the rate of cell replication error. During embryogenesis, the zygote divides to form blastomeres, or groups of cells that become distinct germ layers and ultimately give rise to organs. Developing cells could approach this process from one of two extremes: either a cell may be entirely autonomous, adhering to a genetic or epigenetic program in which the fate of each daughter cell is encoded in the DNA or DNA modification state of its precursors, or a cell may rely heavily on environmental cues to specify its course of action. In the latter case, signals serve as a local selection pressure differentially amplifying the proportion of a given cell type. Development in most vertebrate organisms relies heavily on selection signals to make both proliferation and fate-specification decisions (Watt and Hogan, 2000; Kurokowa et al., 1987). On the other hand, the cells of simpler organisms are virtually impermeable to such external signals. Development in some species of leeches proceeds in this rather rigid way (Stent and Weisblat, 1985).

The evolutionary origin of cell-signal sensitivity during development might be explained either in terms of robustness or in terms of coding capacity. Selection pressures to minimize the coding capacity of the genome will tend to promote cellular responsiveness to external survival signals, allowing the breadth of a cell's genetic repertoire to be reduced whereas community diversity increases. Such a strategy is evident in the human distal gut microbiome (Gill et al., 2006) and in the hindgut microbiota of wood-feeding termites (Warnecke et al., 2007). The gut microbiome is significantly enriched in a large number of compounds critical for microbial survival, no complete set of which is synthesized by a single genome. These examples are derived from large communities of symbiotic single celled organisms rather than multicellular organisms. Multicellular organisms however represent a special case of a large community of symbiotic cells—consisting largely of clonal cells—and we might anticipate observing a similar pattern.

Having said this, in eukaryotes, where replication rates are not limited by genome size, coding capacity is less likely to be important and robustness considerations more important. Environmental responsiveness can increase robustness by allowing for the possibility of a 'majority rules' mechanism for error correction. If a cell makes an error in replication, neighboring cells could induce it to return to its normal state. Sensitivity to fluctuations can also be reduced through signaling cascades whereby continuously varying inputs come to be expressed discretely in populations of cells (Ferrell, 1999; Krishnamurthy et al., 2007). Adult stem cells, defined as cells capable of long-term self-renewal and a plurality of lineage potentials (Schofield, 1978; Spangrude et al., 1991), generally reside in a niche, or microenvironment, that supplies necessary trophic factors to initiate proliferation and maintain cells in an undifferentiated state (Kurokowa et al., 1987; Watt and Hogan, 2000; Varnum-Finney et al., 2000). This arrangement is commonly understood to be an adaptation to diminish the risk of uncontrolled cell growth, such as in cancer (Fuchs et al., 2004).

We suspect that the capacity to autonomously or signal-dependently undergo development (which we operationalize in terms of proliferation and differentiation) is an evolutionarily significant, and perhaps, defining characteristic of an organism (Colman-Lerner et al., 2005). Whereas some lineages show a uniform preference for autonomy or somatic signals, some closely related species exhibit different degrees of cellular autonomy during development. For example, one species of sea urchin, develops an oral–aboral axis autonomously, whereas a sister-species requires the influence of several cytokines to develop equivalent structures (Wikramanayake et al., 1995). Most vertebrates rely heavily on intercellular communication early in embryogenesis, but disparities in the degree of autonomy exist between vertebrate cells at different stages of development (Li and Neaves, 2006).

Upon completion of development, organisms require a mechanism to continually replace damaged cells. In this processes, cell lineage commitment, differentiation, proliferation, and death rates must be coordinated so as to minimize the rate of error (Fuchs and Segre, 2000; Wagers and Weissman, 2004). The models we shall propose are based on a simple system of stem cell self-renewal and differentiation that occurs in either embryonic development or adult maintenance. The models describe cell development in terms of the rates of error, which we define in terms of a skewing of cell density in the process of proliferation and differentiation. The models can be analyzed in four different forms, each corresponding to a different category of cell–environment interaction.

3. Dynamics of the cell lineage

3.1. Somatic niche dynamics with construction

The general form of the developmental model is as follows:

$$\dot{x}_i = \sum_{j=1}^{N} (f_{ij} x_j - x_i d_{ij} x_j), \tag{1}$$

where x_i are the densities of cells of developmental state (or cell-type) i and f_{ij} expresses transitions among developmental states as a function of signals constituting the somatic niche. Signals modulating death rates among compartments i and j are captured by the rate constants d_{ij}. The transition function can be written in

a general form as

$$f_{ij} \equiv f_{ij}(\Sigma) = f_{ij}\left(\sum_{j=1}^{N} q_{ij}x_j\right). \tag{2}$$

Hence transitions rates are determined by programmed transition probabilities (q_{ij}) and signals produced by cells in the target state j (Fig. 1).

We consider four different developmental scenarios, where each differs in the production and sensitivity to somatic signals and the density of different cell types. The first two scenarios assume 'global' density dependence where all cells are in competition and only a single lineage persists. The second two assume local density dependence among cells in the same developmental stage, which corresponds to multilineage differentiation. In each case of density regulation we consider both global signals generated by the cells capable of influencing all cells (extrinsic signals), and local signals feeding back to influence only those cells generating the signal (intrinsic signals) within a single proliferating compartment.

	Local competition	Global competition
Local signaling	LS–LC	LS–GC
Global signaling	GS–LC	GS–GC

In the table above, rows represent somatic signals and the columns the form of the density-dependent competition. The terms in the table correspond to modifications of the general dynamics to render a specific mechanism of density regulation and signaling:

LS–LC: $q_{ij} = 0$ for $i \neq j$; $q_{ii} = 1$; $d_{ij} = 0$ for $i \neq j$; and $d_{ii} = d$, which yields the purely local dynamics

$$\dot{x}_i = \sum_{j=1}^{N} f_{ij}(x_i)x_j - dx_i^2. \tag{3}$$

LS–GC: $q_{ij} = 0$ for $i \neq j$ and $q_{ii} = 1$, $d_{ij} = d$, which yields the local signal (intrinsic signal) and global density regulation dynamics

$$\dot{x}_i = \sum_{j=1}^{N} (f_{ij}(x_i)x_j - dx_i x_j). \tag{4}$$

GS–LC: $q_{ij} = 1$, $d_{ij} = 0$ for $i \neq j$ and $d_{ii} = d$, which yields the global signal (extrinsic signal) and local density regulation dynamics

$$\dot{x}_i = \sum_{j=1}^{N} f_{ij}(\cdot)x_j - dx_i^2. \tag{5}$$

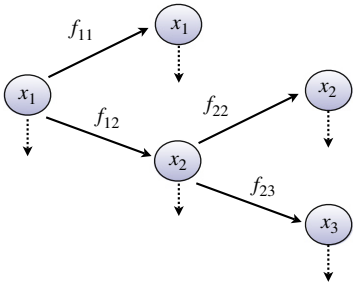

Fig. 1. Schematic representation of the developmental tree. The density of a given cell type is denoted by x_n. Cell type i can make a forward transition to a new type j at a rate proportional to f_{ij}. The decay process is sketched with vertical, dashed arrows. Upward branches of the tree denote proliferation of a cell, and downward branches, differentiation.

GS–GC: $q_{ij} = 1$ and $d_{ij} = d$, which yields the purely global dynamics

$$\dot{x}_i = \sum_{j=1}^{N} (f_{ij}(\cdot)x_j - dx_i x_j), \tag{6}$$

where the argument $(\cdot) = x_1 + x_2 + \cdots + x_N$.

The function $f_{ij}(\Sigma)$ is defined as

$$f_{ij}(\Sigma) = \begin{cases} 1 - \exp[-pr(k+\Sigma)] & \text{if } i = j, \\ \exp[-pr(k+\Sigma)] & \text{if } i = j+1, \\ 0 & \text{otherwise.} \end{cases} \tag{7}$$

The parameter r is the developmental error rate which modifies the value of p, hence there is no developmental error when $r = 1$. A value $r = 1$ implies that the balance between proliferation and differentiation is controlled by the parameter p. As r approaches 0 a greater number of cells undergo differentiation erroneously, skewing the population of cells toward the lower branches of the differentiation tree. The parameter d is the density constant which determines the half life of the cell when in competition with other cells for their cellular signals. The parameter p the proliferation rate, and N the number of cell types or developmental stages. The parameter k, assumed to be small, modulates the proliferation rate in the absence of feedback. The sum $\sum$ is defined in Eq. (2). Thus in this model the somatic environment is able to influence both the growth rate and the death rates.

3.2. Somatic autonomy

We establish an autonomous reference case to provide a null model where the f_{ij} does not depend on the local somatic signals, which corresponds to $\Sigma = 0$ in definition (7). We denote the density in this case as $y \equiv x(\Sigma = 0)$. We use this condition as a dynamic reference for all those models that include some form of signal dependence.

4. A developmental error function

We can use the models presented in the previous sections to measure the deviation from a developmental 'target' —the stationary distribution of the dynamics for an error-free control system. In this section we present a means of calculating the 'robustness' (the inverse of the deviation of the system trajectory upon perturbation of causally relevant components) of the signal dependent and autonomous dynamics, in order to determine which one of these two strategies is more likely in a given parametric context. We do not model the evolution of the optimal solution explicitly. We restrict ourselves to establishing the strategic costs and benefits of alternative developmental plans.

Firstly, we define the stationary solutions for the signal-dependent, x, and autonomous systems, y, as

$$\hat{x}(r) = x(t \to \infty, r), \tag{8}$$

$$\hat{y}(r) = y(t \to \infty, r), \tag{9}$$

and the Euclidian relative distance between the solutions with and without error ($x(r)$, $y(r)$ and $x(1)$, $y(1)$) as

$$\mathscr{D}_x = \left[\frac{x(r) - x(1)}{x(1)}\right]^2 = \left[\frac{x(r)}{x(1)} - 1\right]^2, \tag{10}$$

$$\mathscr{D}_y = \left[\frac{y(r) - y(1)}{y(1)}\right]^2 = \left[\frac{y(r)}{y(1)} - 1\right]^2. \tag{11}$$

Notice that $\mathscr{D}_x$ and $\mathscr{D}_y$ refer to the distance to a state without error, controlling for the signaling dynamics—those that respond to somatic signals and those that do not. We shall refer to the

error function, H, as the difference between these two quantities

$$H = \mathscr{D}_y - \mathscr{D}_x. \tag{12}$$

From the previous definition it is clear that when the error function is positive, the system is more robust when sensitive to feedback from somatic signals in the somatic niche. The opposite applies when $H<0$.

4.1. A simple illustrative example

The dynamical systems introduced in the previous sections are highly nonlinear and N-dimensional. In order to better understand the dynamics of autonomy and signal selection, we first consider the one-dimensional case. Since we are dealing with one dimension of cells we cannot speak of errors of differentiation but errors in the regulation of cell density. Hence signals serve as a density compensation mechanism. The system of equations is given by

$$\dot{x} = (1 - \exp[-pr(1+x)])x - dx^2, \tag{13}$$

for the case with environmental feedback, and

$$\dot{y} = (1 - \exp[-pr])y - dy^2, \tag{14}$$

without it. The stationary solution for these dynamics is given by

$$\hat{x}(r) = \frac{1}{d} + \frac{1}{pr}\mathscr{W}[\alpha(p,r)], \tag{15}$$

$$\hat{y}(r) = \frac{1 - \exp[-pr]}{d}, \tag{16}$$

where the function $\mathscr{W}$ is the Lambert function or product log evaluated at its principal value, defined as the inverse of $f(\mathscr{W}) = \mathscr{W}e^{\mathscr{W}}$ where $\mathscr{W}$ is any complex number. The function $\alpha(\cdot)$ is defined as

$$\alpha(p,r) = -\frac{pr}{d}\exp[-pr(1+1/d)]. \tag{17}$$

Using these expressions we can compute the distances

$$\mathscr{D}_x = \left[\frac{d}{r}\left(\frac{r\mathscr{W}[\alpha(p,1)] - \mathscr{W}[\alpha(p,r)]}{p + d\mathscr{W}[\alpha(p,1)]}\right)\right]^2, \tag{18}$$

$$\mathscr{D}_y = \exp[-2pr]\left(\frac{\exp[p] - \exp[pr]}{\exp[p] - 1}\right)^2. \tag{19}$$

Fig. 2 illustrates the values of H (Eq. (12)) as a function of the error rate r for three different density dependent values of d corresponding to diminishing death rates of the cell. Recall that high errors correspond to values of $r = 0$. For cells experiencing weak density dependence ($d = 0.1$), somatic signals provide an effective robustness mechanism over a wide range of rates of developmental error. Only when there is no error ($r = 1$), and at very high rates ($r \approx 0$), do the differences between the autonomous and signal-dependent stationary solutions become minimal. As the competition becomes stronger and the cells shorter lived, the volume of phase space associated with error rates canalizing the distribution of cell types contracts. At very high rates of error, signal sensitivity cause the cells to deviate more significantly from the developmental trajectory than under the autonomous strategy. Hence in populations of long-lived cells, experiencing weak competition, somatic selection mediated by signals becomes more effective at canalizing development. Autonomy is expected for shorter-lived cells experiencing high errors rates, where somatic signals cease to be reliable and density regulation is very strong.

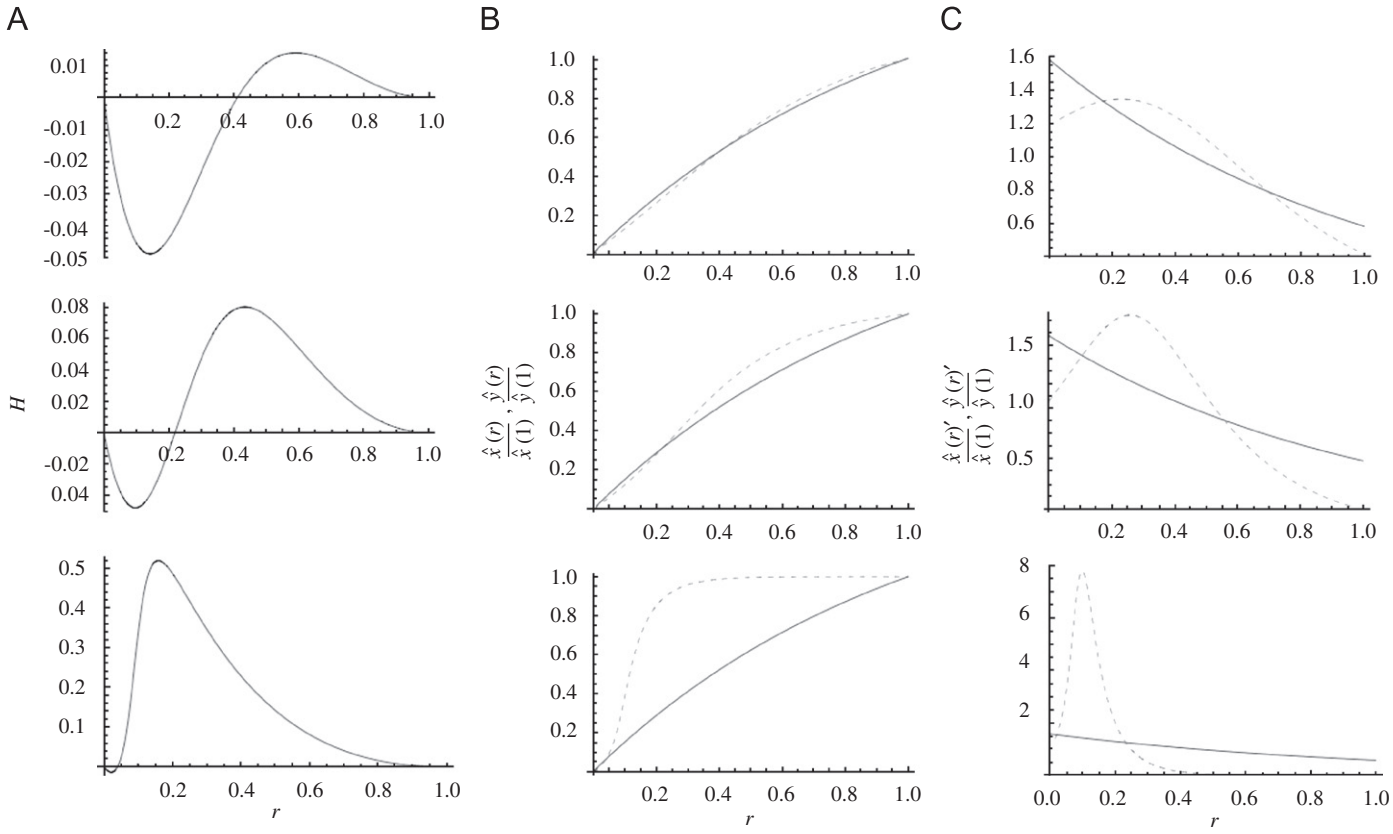

Fig. 2. (A) The error function, (B) the normalized stationary densities of x (dash) and y (full), and (C) the normalized derivatives of the stationary densities of x (dash) and y (full). All plotted as a function of r for three values of density dependence: $d = 0.1$, 0.5, and 1, reading from the top to the bottom panels. (A) Decreasing the signal induced density dependence d causes the somatic niche to minimize the impact of fluctuations (or errors) in the developmental trajectory (a greater volume of the error function above 0). (B) The density of x becomes greater than y for a larger range of values of r for higher values of d. (C) Small variations in r induce large changes in the steady state values of x but not of y. We assume values of $p = 1$ and $k = 1$ throughout.

These results depend on few free parameters and are expected to be rather general.

4.2. Dynamics of multiple cells types

Now, we consider the complete set of N-dimensional equations treating multiple cell types. The full system exhibits characteristics similar to the one-dimensional system presented above, but some important consequences of expanding the number of cell types emerges as well as allowing for global density regulation. Precise parameter values cannot be obtained from empirical systems, but the structure of the equations allow us to explore the full range of continuous parameter variation. Figs. 3–5 illustrate the error function in the $r-d$ plane. In Fig. 3 we plot the same value of the error function in three different ways, in order to justify the choice of four contour levels in Figs. 4 and 5.

Each of the panels in Figs. 4 and 5 (each comprising four phase portraits) represents one of four different permutations of local and global signaling and density regulation. Different regions in the parametric state space are color coded, reflecting different values of the error function. In the black and white regions either somatic autonomy or somatic signals strongly increase canalization (minimize deviation from the error-free distribution). The dark and light gray regions represent quantitatively similar values (near zero) but autonomy is slightly favored in the darker regions and somatic signals in the lighter regions.

In the local signal–local competition dynamics, somatic signals are favored over a wide range of developmental errors and for on average, shorter-lived cells (high d). At high rates of cell proliferation, somatic signaling is strongly favored. When the number of different cell types is large, islands of strong signaling benefit arise, surrounded by regions of relative indifference. At the highest error rates, autonomy more effectively minimizes error, canalizing development more effectively than somatic signaling. At these error rates almost all the cells are differentiating and the signal is unable to restore the population composition to its error-free state. In Appendix we plot the values of x and y independently in order to provide a more intuitive insight into the behavior of the error function.

A similar pattern is present in the global signal–local competition dynamics. However, the regions of high somatic signal benefit and autonomy contract and the region of weak signaling benefit expands. Cells do not benefit from the global majority-rule selection process and must make do with cells of a single type.

The local signal–global competition and global signal–global competition dynamics are approximately equivalent as a result of the strong controlling influence of the global density regulation across multiple cell types. At low rates of proliferation the autonomous solution dominates the state space, with an island of strong autonomy at intermediate errors and for long-lived cells. Strong density dependence is what we might expect when all cells are dependent on a single resource for survival, without much modularity in development. At high rates of proliferation and weak density regulation (weak global competition) with lower error rates, the somatic signaling strategy emerges as the most effective strategy.

We can also determine the influence of varying the sensitivity to signals on the behavior of the error function. This is illustrated in Fig. 6. We find that by allowing the signal feedback sensitivity (γ) to vary continuously (varying the density dependence), we generate a similar effect to varying the number of cell types. However, this is only true for the growth rate and not for the death rate. Hence an increased sensitivity can increase the range of error rates over which signaling is favored by decoupling the population advantage of signals influencing growth rates from their increased cost in terms of competition with an increased number of cells.

5. Discussion

The information required to specify cell fate can be encoded in the genome or provided by the cellular environment. Both sources of information are typically exploited during development. When there are errors in development, majority-rule mechanisms acting at the population level, are able to overcome errors experienced by individual cells (Krakauer and Plotkin, 2002). Majority-rule mechanisms tally the population 'preference' for a given cell state, and enforce this state uniformly. These mechanisms require a means of coordinating decision making, and this can be achieved through a signal that modifies the local somatic environment, or somatic niche, establishing a local selection pressure favoring a given cellular composition. For large populations of cells, one general class of robustness mechanism makes use of selection processes analogous to Darwinian selection in populations of organisms (Weissman, 1903; Buss, 1987; Klekowski, 1988; Krakauer and Pagel, 1996; Kirschner and Gerhart, 1998). Cells collectively contribute to constructing a signal-based selection pressure during development, a selection arena (Stearns, 1987), biasing the population of cells back toward a baseline developmental distribution obtained without perturbation.

We have performed a sweep of potential parameter values (sensitivity analysis) in order to characterize a full range of

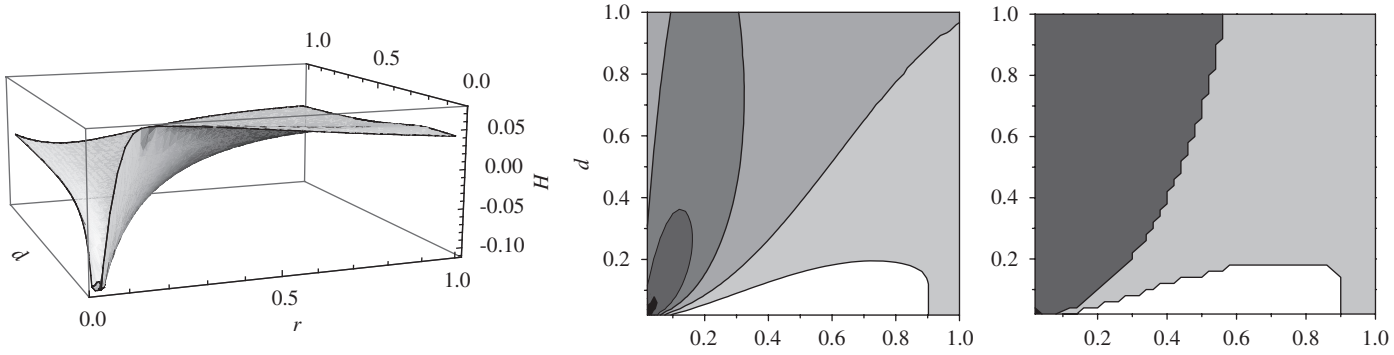

Fig. 3. Three representations of an identical error function H in the $r-d$ phase plane assuming local selection and local competition dynamics (LS–LC). In the three-dimensional surface plot the surface is shaded in order to reveal curvature. In the two contour plots the darker regions favor autonomy whereas the lighter regions favor somatic signals. In the far right plot only four contours are illustrated: two levels for the full range of error values within 10% of the total variance of the error function above and below the zero plane, and two levels for all remaining values beyond 10% of the variance of the error function. This is more revealing than the full contour plot in the central panel because much of the surface has a similar value (relatively flat) as shown in the three-dimensional plot.

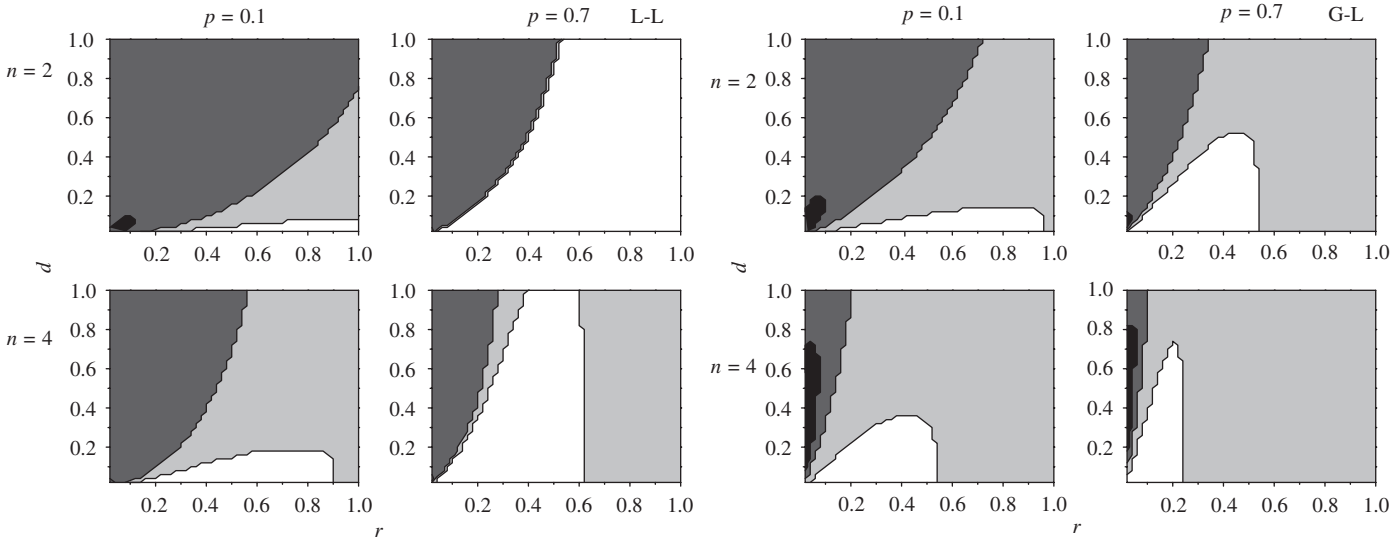

Fig. 4. Phase plane $r-d$ illustrating four different regions for which selection through somatic signaling or developmental autonomy are best choices in order to canalize development, or minimize deviation of a developmental trajectory from an error-free trajectory, as a function of rates of cellular proliferation and variation in the number of cell types. Black regions strongly favor autonomy. Dark gray regions weakly favor autonomy. White regions strongly favor somatic signals. Light gray regions weakly favor somatic signals. Both sets of panels describe the results of dynamics with local density regulation.

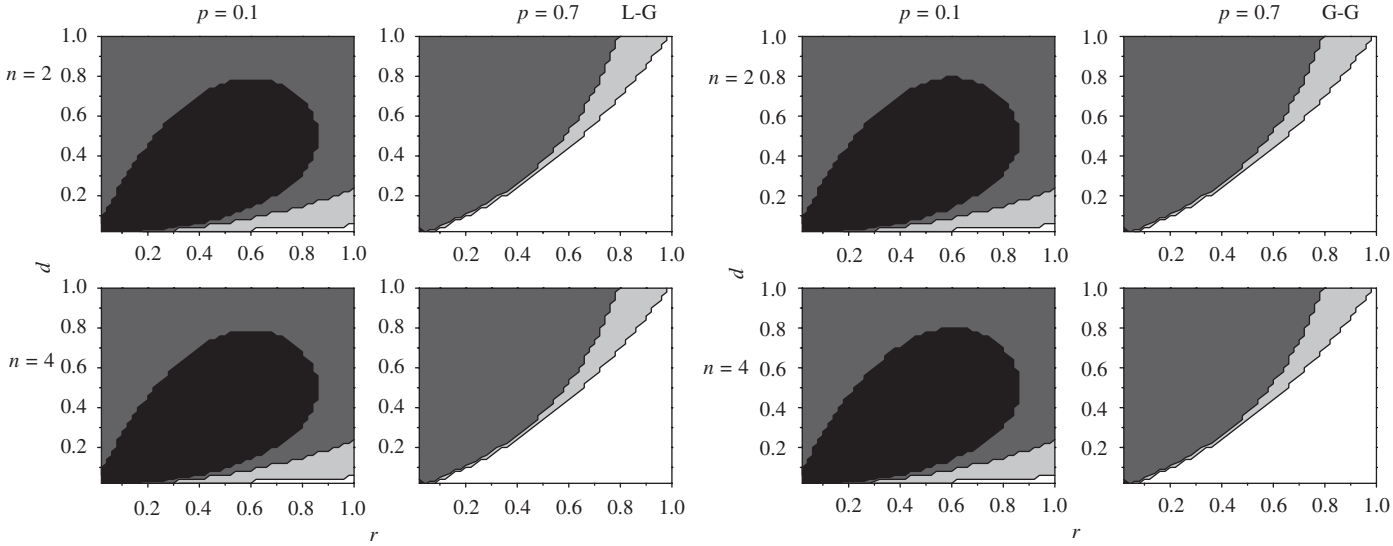

Fig. 5. Details identical to previous panel. Both sets of panels describe the results of dynamics with global density regulation.

different developmental strategies. We find that when cellular competition is localized, through modularity for example, which might be created by basement membranes, multiple selective arenas can be established. In these arenas at mid to low error rates (on the order of a 50% or less deviation from a baseline developmental program) somatic signals promoting cellular selection provide a consistent advantage over signal insensitivity (autonomy). Signals are able to compensate for deviations that skew division towards excessive differentiation and promote a coherent binding to a desired developmental trajectory. Signals acting as growth factors or survival factors compensate for the reduction in proliferation following from developmental errors. The adaptive value of signals is derived from the 'wisdom of the cellular colony', making use of the average differentiation state of the population of cells.

In the remaining section we discuss briefly a few empirical examples concerning the issues of autonomy and signal dependence for cell type determination, cancer progression, and the aging of a lineage. Since the precise parameter values for somatic signaling during development are not known, whereas the model phase space is effectively characterized, we seek to place several developmental systems within the autonomy-sensitivity strategy space according to qualitative trends reported during differentiation.

1. *Adaptive immunity: signal-dependent and autonomous T-cell proliferation*: In the production of cells of the adaptive immune system, it is understood that antigen is required for clonal selection, leading to affinity maturation of the T cell receptors. Antigen acts as a signal, promoting differential survival of T cell lineages in the thymus. More recent research has emphasized autonomy in the production of the cytotoxic T cell receptors, which upon encounter with antigen, undergo several rounds of programmed proliferation (Kaech and Ahmed, 2001) independent from continued antigen exposure. In the generation of specificity, the antigen signal is essential and serves to both

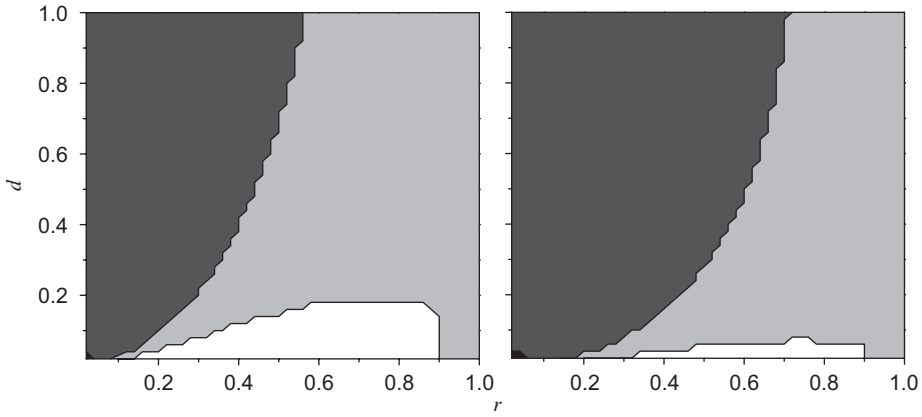

Fig. 6. The influence of signal sensitivity on the error function assuming a LS–LC mechanism. We consider functions of the form, $\dot{x} = 1 - \exp[-pr(k + \gamma x)] - dx$, where the γ parameter allows for continuous variation in the strength of the signal feedback. On the left $\gamma = 1$, and on the right $\gamma = 0.4$. Signal sensitivity behaves an analogous way to varying the number of cell types: increasing sensitivity is approximately equivalent to increasing the number of cell types on the growth rate but has no influence on the death rate. Hence greater sensitivity allows for a lower overall rate of error and increases the range of parameter values over which signaling is more robust than autonomy.

amplify desirable receptor types and eliminate self-reactive types. One explanation for autonomy is as a mechanism to promote continued differentiation even with low levels of virus. In theoretical work, this mechanism has been shown to lead to more effective virus clearance (Wodarz and Thomsen, 2005).

Our results suggest another possible explanation for the observed signal-independent proliferation. According to our models, autonomy is favored both at very high error rates, and when there is a global density regulation. If the early rounds of division following antigen stimulation are likely to lead to an excessive production of inappropriate receptors (r approaches 0), then there would be an early benefit for a programmed, autonomous response. Furthermore, if the population of cells in the thymus is homeostatically controlled by some form of density regulation early in proliferation (corresponding to a higher value of d), then autonomy might be favored as a means of promoting the persistence of a greater diversity of receptor types. Selection would be undesirable as it could lead to a premature reduction in adaptive variance.

To allow this alternative hypothesis to be consistent with our models, cells should be responsive to signals generated by cells of similar type. This is because we assume that the population of dividing cells generates the differentiation and proliferation factors. There is some evidence for this from the cytokine, interleukin 2 (IL-2), which is produced by activated T cells, and controls proliferation of T cells by inducing transcription of its own receptor (Ullman et al., 1990). For T cells, the balance between the effect of cell-autonomous differentiation programs and extrinsic signals has not been fully characterized, but it has been suggested that epigenetic reprogramming of the T cell following autonomous proliferation can inhibit responsiveness to IL-2, promoting greater autonomy (Reiner, 2001).

2. *Varied signal sensitivity across sea urchin species during early development*: In sea urchins, cell communication plays an important role in cell fate determination whereas the degree of signal dependence can vary widely. In a comparative study of the two species, *Strongylocentrotus purpuratus* and *Lytechinus pictus* it was determined that cells destined to become ectoderm in *S. purpuratas*, are able to differentiate into polarized embryoids without signals secreted by cells constituting the vegetal blastomeres. By contrast, the differentiation of aboral ectoderm cells in *L. pictus*, requires factors secreted by the vegetal blastomeres(Wikramanayake et al., 1995). The average environmental temperature for *L. pictus* is higher than that of *S. purpuratus* (Marsh et al., 2001), which may correspond to a higher rate of developmental error (r). Our models suggest that it would beneficial for the cells of an organism experiencing high rates of error to remain dependent on signaling for a longer period during development; as cells move into regions of higher developmental error, the signaling regime is favored. In this example, different species inhabit different areas of the r–d phase plane; the embryonic *S. purpuratas* cells exist in a regime that favors relative autonomy, while those of *L. pictus* would be placed in a region of signal sensitivity.

   In the related studies it has been reported that although *S. purpuratas* embryos possess autonomy with respect to the vegetal blastomeres, they are supported by a 'community effect' whereby large populations of similar cells are able to compensate for the lack of signals. Thus they demonstrate a local rather than a global signal sensitivity. Further evidence for this effect derives from large aggregates of cells that survive at higher rates than smaller aggregates (Khaner and Wilt, 1990). In species where the number of different cell types is relatively small (low value of n) and the proliferation rate (p high), there is a benefit associated with remaining sensitive to signals (Fig. 4, top left panel).
3. *Local signaling in meristematic plant tissues*: In higher plants, lateral organs, such as leaves, are generated by the shoot apical meristem (SAM). During ontogeny, there is continuous contact between the undifferentiated tissue of the SAM and the external (above ground) structures that develop from these tissues. The SAM comprises three layers, from the outermost L1, to L2 and L3. When the growth of the outermost layer of the SAM (L1 which gives rise to epidermis) is restricted by selective CDK inhibitors, the epidermis exhibits larger cell size, proportionately fewer cells, and diminished leaf size. The inner two layers of the SAM (L2 and L3) responsible for the mesoderm, are observed to function autonomously from the outer layer, and are unaffected by L1 inhibition (Bemis and Torii, 2007). This corresponds most closely to our model of local–local dynamics in which compartments respond only to signals from the same cell type. The logic behind the autonomy of developmental layers would be that errors are minimized by partitioning potentially, cascading sources of error. This is exemplified in our models through the greater preference for autonomy when density regulation is global than when it is local (Fig. 4).

4. *Signal independence and cancer*: A common cause of cancer is a loss of dependence on extra-cellular signals for cell survival, facilitating cell migration (Yamaguchi et al., 2005). Similarly, the over-expression of cell adhesion molecules, such as the integrins can promote the detachment of tumor cells from their tissue (Ramsay et al., 2007). We can think of this as a cell becoming autonomous, when for the sake of organismal health, it should remain signal dependent. Only at very high rates of error ($r \approx 0$), does healthy development favor an autonomous strategy as no cells can be relied upon to signal accurately. Cancer cells lose sensitivity and thereby deviate from the cellular composition favored by the population of cells as a whole.
   For example, chronic myelogenous leukemia (CML) is caused by a translocation of genes resulting in uncontrolled myeloid cell production. This excessive proliferation is induced by a tyrosine kinase activity of the translocation (BCR-Abl) gene product. The gain of function mutation abrogates dependence on externally derived growth factors in favor of an internal signaling enzyme (Sattler and Salgia, 1997). Thus the loss of sensitivity is the primary cause of the transformation of the healthy cell to a cancerous state.
   The population of cells can be skewed back to growth-factor dependence through the use of the drug ST1571 which inhibits the tyrosine kinase activity of the translocation (BCR-Abl) gene product (Salesi et al., 2003) killing the cells. However, BCR-Abl cells are differentially sensitive to the tyrosine kinase inhibitor activity of ST1571. In the absence of the compound, resistant cells proliferate at a rate 30% slower than ST1571 sensitive cells. Ten times the concentration of ST1571 is required for a 50% reduction in cell number of the resistant cells as opposed to the sensitive ones (Mahon et al., 2000). This shows that for such cancerous cells, autonomy comes at a cost. When conditions favoring autonomy (as in the addition of ST1571) are not present, cells are likely to be out-competed by cells that preserve signal sensitivity. This experiment nicely illustrates how cancer cells, by following a locally optimum strategy can deviate from the tissue optimum, and that when the transformed cell no longer possess resistance, the tissue collectively can competitively exclude these cells.
   Our model suggests that organisms may have mechanisms in place to prevent cells from straying from the 'beneficial' regions of the r–d phase plane. Somatic signals impose a cost of autonomy which in the case of successful cancer represents the cell's circumvention of such constraints.
5. *Aging and ontogenetic variation in signal sensitivity*: In chicks, bone morphogenetic protein-2, BMP-2, stimulates the differentiation of neural progenitor cells into mature neurons. When embryonic nerve cells from different developmental stages are transplanted into chick embryos, the younger cells exhibit a tenfold higher level of sensitivity to BMP-2, as exhibited by the number of tagged differentiated neurons in the chick. Younger cells demonstrate a greater signal dependence and the older cells an increased autonomy. The increased autonomy could result from a time-dependent change in the neuronal precursor cells, or selection for a sub-population of cells less sensitive to differentiation factors (White et al., 2001). However, it has been observed that neural stem cells come to rely more upon autonomous programs for differentiation as they progress through development (Edlund and Jessell, 1999). This is analogous to the example with the two different species of sea urchin; in that case, two species came to inhabit different regions of the r–d plane over evolutionary time, whereas here, an individual organism traverses the plane during its lifetime. Assuming that later developmental stages accumulate more errors, the aging process would correspond to a movement along the negative diagonal axis of the r–d phase plane (Figs. 4 and 5)—from the lower right quadrant to the upper left (increasing r and d). This would generate a concomitant switch from a signal sensitive to an increasingly autonomous, developmental strategy, as suggested by the developmental change in signal sensitivity of neural progenitor cells.

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Appendix

To provide greater intuition into the functional form of plots 2–5 we plot the densities x and y independency in Fig. 7.

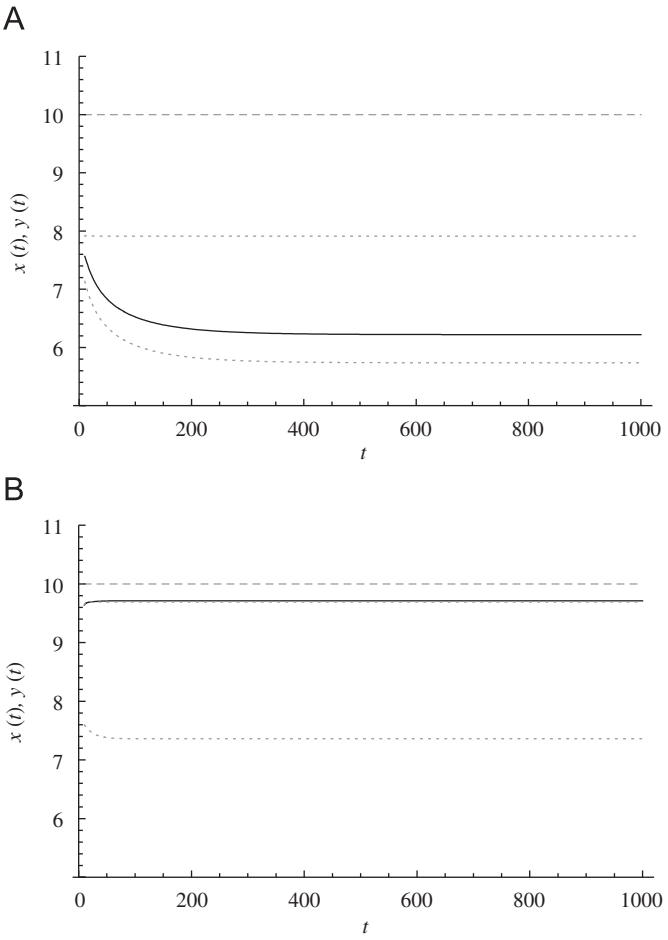

Fig. 7. The dynamics of sensitive (x) and autonomous (y) cell population densities assuming local signaling and local competition. (A) Low error regime ($r = 0.6$). The solid curve assumes signals with error and the dashed curve signaling without error. The dot-dash is the no signal with error and the dotted curve no signal without error. (B) High error regime ($r = 0.1$). Key to curves as before. In both plots we set $p = d = 0.1$. In the low error regime the relative difference in the error free and signal with error dynamics are significant such that signaling is associated with a lower population density than no signaling. In the high error regime, the signaling strategy has a significantly increased population density, raising it far above the no signaling densities.

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