A gene network model of resource allocation to growth and reproduction

George Marnellos
Sloan Center for Theoretical Neurobiology,
The Salk Institute, La Jolla, CA 92037, USA

Eric Mjolsness
Machine Learning Systems Group,
Jet Propulsion Laboratory,
Pasadena, CA 91109, USA

Abstract

We present a model of optimal allocation of resources to reproduction and growth in a simple multicellular organism with limited lifespan, using a gene network formalism to simulate gene interactions within cells. The model is compatible with more conventional approaches to allocation problems in life history and in addition provides connections between processes at the gene and cell levels on one hand and life history strategies on the other. The model may offer an example of how a genotype orchestrating development imposes constraints on the optimal solutions that evolution can reach.

Introduction

How an organism uses energy and other resources extracted from the environment to promote its survival and growth, produce offspring or store for future needs is crucial for the organism's fitness. Life-history traits of an organism, that determine when and in what proportions the organism allocates resources during its lifetime, include age and size at first reproduction, number and size of offspring and life-span; all these traits and others have been studied both theoretically and experimentally (Roff 1992; Stearns 1992). A particular line of theoretical work in this area has explored optimal allocation of resources to maintenance, storage, growth and reproduction (Gadgil & Bossert 1970; Cohen 1971; Vincent & Pulliam 1980; Kozłowski 1992). Analytical models on this question have relied largely on methods from optimal control theory (Perrin & Sibly 1993) to locate the sought optima. In these models the state variables are high level phenotypic traits like amount of reserves, size of vegetative and reproductive parts and other such subsystems of an organism, and what is optimized is the proportion of resources allocated to each subsystem at each age. Stochastic optimization techniques have also been used in optimal allocation models (Blarer & Doebeli 1996).

Although such models have dealt with growth of organisms, they have not considered the effects of development and the constraints it might impose on the evolution of life-history traits. In order to address questions about how development determines what life-history strategies are reachable by optimization, and about what influence cell-level events during development may have on evolution towards optimal phenotypes, we have constructed a model of optimal allocation of resources in a simple multicellular organism with limited lifespan. Our model deals explicitly with life history questions as have been formulated in the evolutionary biology literature and uses a fitness measure from this literature to evaluate the organism's strategy for growth and reproduction. The genetic and cellular interactions of the model are based on the modeling framework which was introduced in (Mjolsness, Sharp, & Reinitz 1991) to simulate developmental processes through the use of regulatory gene networks; this framework has been previously used in a preliminary attempt to explore the effects of developmental gene interactions on the evolution of a multicellular phenotype (Mjolsness *et al.* 1995).

Model

Our model examines growth and reproduction of a simple multicellular organism with limited lifespan; the organism starts as a single cell (equipped with a certain amount of resource reserves) and grows by cell divisions; cells may differentiate into propagule cells which are considered to be the progeny of the organism. No specific geometry has been assumed for the organism: the cells can be thought to form an aggregate of non-interacting units.

Gene net framework. The modeling approach which we have used to represent gene regulation, and which we will be referring to as the *gene net framework*, uses recurrent neural nets to represent state variable dynamics, and a set of rules, a grammar, to represent interactions within and between cells. Our model has five rules: one for non-dividing vegetative cells (e.g. cells in phase G1 of interphase), one for vegetative cells entering mitosis, two rules for cell division (symmetric and asymmetric partitioning of gene products to daughter cells) and one for differentiation from vegetative cell to reproductive propagule. For a detailed description of the gene net framework see (Mjolsness, Sharp, &

Reinitz 1991) and for shorter versions (Marnellos 1997; Marnellos & Mjolsness 1998).

Resource production and allocation. Gene product concentrations are state variables in our model and, through the control of cell divisions, determine how organism size (S), another state variable, changes over time. They thus determine events like resource extraction from the environment and also propagule formation, and consequently control allocation of resources to vegetative growth and reproduction. *Surplus energy* (E), i.e. energy and other resources not used for maintenance, is an allometric function of size $E = \alpha S^{\gamma}$, where $\alpha = 0.12$ and $\gamma = 0.80$; we refer to surplus energy also as *production*. Surplus energy is added to the *reserves* (R) of the organism, another state variable; every time the organism increases by a certain number of cells, an amount proportional to that number is subtracted from the reserves; the same occurs when a propagule leaves the organism equipped with an amount of resources, this amount being a parameter of the model that may be thought of as offspring size. The currency unit used to measure reserve and production amounts in these transactions is the amount of resources needed to make one cell, so one cell "costs" one reserve unit.

Mortality and fecundity. The maximum lifespan of an organism is a number Ω of time steps over which we examine its growth and reproduction (and integrate the differential equations describing the changes in state variables); in our simulations this is $\Omega = 100$. There are two sources of mortality in the model: *extrinsic* and *intrinsic*. Extrinsic mortality μ_e at age (time) t is the probability that the organism will die at that age due to external factors and in our simulations is constant with age; intrinsic mortality is a decreasing sigmoid function of reserve levels (the lower the reserves, the higher the mortality) and is given by

$$\mu_i(t) = \frac{e^{-bR_s(t)}}{1 + e^{-bR_s(t)}} \tag{1}$$

where $R_s(t)$ is the quantity of reserves per cell at time t and b is a positive constant. With these mortalities the *survival* function $l(t)$, i.e. the probability that an organism will survive to a certain age t, is given by the decreasing function

$$l(t) = \prod_{\tau=1}^{t}(1-\mu_e(\tau))(1-\mu_i(\tau)) = (1-\mu_e)^t \prod_{\tau=1}^{t}(1-\mu_i(\tau)) \tag{2}$$

for constant extrinsic mortality μ_e.

Fecundity $m(t)$ is given by the number of propagules that are produced at age t. Propagules survive and give rise to a new organism with probability Pr that is an increasing function of propagule size S_p, i.e. the amount of reserves that a propagule is equipped with when it leaves the parent organism (S_p is the same for all propagules and constant in time),

$$Pr(S_p) = \frac{C_1}{1 + e^{-S_p}} - C_2, \tag{3}$$

where C_1 and C_2 are positive constants — we have used $C_1 = 1.8$ and $C_2 = 0.8$, but any values that result in a concave increasing function with range between 0 and 1 would do. Thus effective fecundity $\tilde{m}$ at age t is taken to be the product of number of propagules produced at that age times propagule survival probability

$$\tilde{m}(t) = m(t)Pr(S_p). \tag{4}$$

The amount of propagule reserves becomes the initial amount of reserves of the organism that the propagule gives rise to. We allow negative reserve levels up to 30% of an organism's size; this would correspond to an organism under severe resource shortage that has started using up components of its cells as nutrients. When reserves fall below –30% of size, mortality becomes 1 and the organism is not considered further.

Fitness and objective functions. The fitness measure we maximize by optimization is the lifetime offspring production of the organism $R_0 = \sum_{t=1}^{\Omega} l(t)\tilde{m}(t)$, where Ω is maximum lifespan, $l(t)$ survival to time t (Eq. 2) and $\tilde{m}(t)$ effective fecundity at time t (Eq. 4). The objective function of this problem also contains a quadratic penalty term which is minimized and tends to make all propagules of the organism have gene product concentrations identical to those of all the other propagules and of the founder spore cell that gave rise to the organism; this term we refer to as *identical propagule cost*, I:

$$I = \sum_{i}^{propagules} \sum_{j}^{genes} (v_j^i - v_j^F)^2 \tag{5}$$

where v_j^i is concentration of gene product j in propagule i and v_j^F is concentration of the same gene product in the founder cell of the organism. Finally there is a quadratic penalty term P (a sum of the squares of all the parameters we optimize on) that prevents the parameters from getting excessively large (in our runs they rarely grow beyond order of magnitude 10^1). All terms of the objective function are weighted, and in our runs we have tuned these weights so as to achieve the best results with the optimization methods used. The objective function we maximize is therefore

$$\max J = w_{R_0} R_0 - w_I I - w_P P \tag{6}$$

where the weights w_{R_0}, w_I, w_P are positive numbers.

The parameters we optimize on are: propagule size, S_p (i.e. the amount of reserves invested in each propagule); initial concentrations of gene products in the founder

cell (spore) of the organism (which, if identical propagule cost I is very small, should be almost identical to those of the propagules that the organism produces); and parameters of the gene network, like gene interaction strengths, thresholds for gene activation, decay rates of gene products, parameters that govern the triggering of grammar rules, and so on. In the case of runs with two (2) genes there are 27 parameters that are optimized on. We have used stochastic optimization techniques to maximize Eq. 6, namely simulated annealing with an efficient temperature schedule and a genetic algorithm implemented in parallel — for a description of these algorithms, as well as a more detailed description of the parameters optimized on, see (Marnellos 1997; Marnellos & Mjolsness 1998).

Results

We have carried out optimization runs with two-gene networks for various strengths of extrinsic mortality μ_e. Illustrations of model simulations using parameter values derived by optimization appear in Figs. 1 and 2. The best solutions (in terms of fitness) obtained in these runs are presented in Table 1. The life history features, apart from fitness, of the solutions listed in this Table are: age at maturity, i.e. age at first reproduction; life expectancy at birth (LE) which is given by $LE = \sum_{t=1}^{\Omega} l(t)$, where Ω is maximum lifespan and $l(t)$ is probability of survival to age t as determined by Eq. 2; *intrinsic life expectancy* which is due to intrinsic factors only, i.e. is calculated as LE but with μ_e assumed to be zero; propagule reserves (or propagule size) S_p; total number of propagules produced during the organism's lifetime; and finally, total reproductive effort, which is the total number of propagules multiplied by the reserves S_p of each propagule.

Solutions of higher fitness tend to produce more propagules but make a smaller reproductive effort. It appears that, because of intrinsic mortality (which increases when reserves fall), the strategy adopted in these solutions is to maintain high reserves throughout and release them in reproductive events towards the end of the maximum lifespan; as a consequence, growth rates are kept low, but intrinsic life expectancies are high for all solutions (in all cases higher than 93, out of a maximum of 100, see Table 1) . However, these solutions are not well adapted to the different levels of extrinsic mortality: reproduction does not shift to earlier times with increasing extrinsic mortality — as has been for instance observed in an analytical model quite close to ours in high level structure (Kozłowski & Wiegert 1987) — or, at least, there is no clear relation between age at maturity and level of extrinsic mortality. In fact, in all but one of the solutions, age at maturity is greater than life expectancy (see Table 1).

In connection with age at maturity, it is interesting to observe that solutions fall into two phenotypes: one

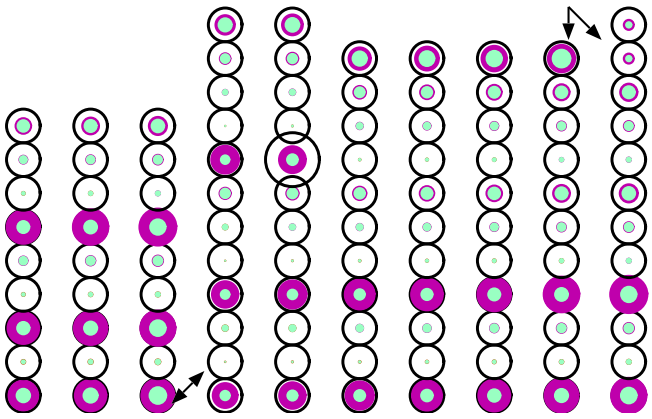

Figure 1: Simulation based on parameters derived by an optimization run, with frames (columns of cells) showing an organism at successive points in time (here are shown time points 51 to 60 out of a maximum lifespan of $\Omega = 100$ time points). The organism has two genes; sizes of the two disks within each cell represent levels of gene products. The larger cell in the 5th column represents a propagule with its reserves. The arrows at the bottom of the 3rd and 4th columns point to an asymmetric cell division: on the left the mother cell and on the right the two daughter cells; the daughter at the bottom receives most of both gene products of the mother (there are other instances of asymmetric division in this Figure which we have not indicated by arrows). The arrows at the top of the 9th and 10th columns point to a symmetric cell division: the daughter cells on the right each receive equal amounts of the two gene products from the mother cell. Note that levels and proportions of gene products are distinct for the cell differentiating into a propagule, for the cell dividing asymmetrically and for the cell dividing symmetrically; gene product levels determine which of these rules is triggered in each instance. In this figure the organism is represented as a column of cells for illustration purposes only (to better illustrate changes in organism size, cell divisions, etc.); in the simulations no specific organism geometry has been assumed and organism cells can be thought to form an aggregate of non-interacting units.

with older age at maturity and smaller propagule size, as is in the solutions in the first column of Table 1 and the top of the second column, and another with earlier age at maturity and larger propagule size, as in the rest of the solutions (see also Fig. 2). This trade-off between propagule size and development time to maturity is a consequence of the fact that, on one hand, a larger size propagule costs more reserves to produce and so tends to reduce future growth and reproduction of the parent and thus fitness, but, on the other, leads to higher growth rates, higher production and so earlier reproduction and higher fitness; conversely, smaller propagule size costs less but leads to slower growth, later reproduction and decrease in fitness. Related to this trade-off is another trade-off between propagule size and propagule number (the smaller the size, the larger the number, and vice versa) which is clearly evident in the solutions of Table 1. These trade-offs are affected by the propagule sur-

μ_e		1	2	3
0.010	**Fitness** (R_0)	**13.7**	**12.4**	**11.7**
	Age at Maturity	88	86	48
	Life Expectancy (LE)	62.3	61.4	59.3
	Intrinsic LE	99.3	97.3	93.8
	Propagule Reserves	1.36	1.21	3.80
	Propagules	58	64	33
	Reproductive Effort	78.9	77.4	125.4
0.013	**Fitness** (R_0)	**10.0**	**9.4**	**8.7**
	Age at Maturity	75	61	64
	Life Expectancy (LE)	54.0	53.7	53.3
	Intrinsic LE	97.4	96.2	95.4
	Propagule Reserves	1.96	2.79	3.99
	Propagules	46	34	30
	Reproductive Effort	90.1	95.0	119.8
0.015	**Fitness** (R_0)	**9.1**	**9.1**	**8.0**
	Age at Maturity	86	64	58
	Life Expectancy (LE)	48.9	48.6	49.2
	Intrinsic LE	94.7	93.6	95.1
	Propagule Reserves	2.26	3.89	3.41
	Propagules	49	39	34
	Reproductive Effort	110.7	151.7	115.9
0.017	**Fitness** (R_0)	**8.0**	**6.7**	**6.5**
	Age at Maturity	89	61	71
	Life Expectancy (LE)	46.4	45.2	45.2
	Intrinsic LE	97.5	94.5	93.4
	Propagule Reserves	1.28	3.84	3.96
	Propagules	72	32	34
	Reproductive Effort	92.2	122.9	134.6

Table 1: Life-history features of the 3 best optimization solutions obtained for various strengths of extrinsic mortality μ_e.

vival function (Eq. 3), which determines how much an increase in propagule size will increase the propagule's chances of survival and thus fitness.

Another salient feature is that life histories in the solutions presented here often include what is called a *bang-bang* switch: after an initial period of exclusive allocation of resources to growth, the organism ceases to grow in size and completely switches to investment in reproduction. This is true for the majority of solutions obtained apart from a few where the switch is more gradual. Both modes of switching have been reported in previous theoretical work (Cohen 1971; Vincent & Pulliam 1980; King & Roughgarden 1982).

All solutions presented in Table 1 differ in the signs and magnitudes of their optimized parameters, which is true even for solutions that are similar in their life-history features (like solutions 1 and 2 for $\mu_e = 0.010$, or solution 3 for $\mu_e = 0.010$ and 2 for $\mu_e = 0.015$). This may indicate that the objective function of this problem (Eq. 6) has many similar optima. The similar life histories that result from different optimization solutions can be considered instances of "phenotypic convergence".

Finally, identical propagule cost, which is not considered in previous resource allocation work, has turned out to be an important component of our model: growth and fecundity in our simulations can be very sensitive to initial concentrations of gene products in the founder cell of the organism. Identical propagule cost may correspond, to a certain extent, to maternal effects described in work on state-dependent life histories (McNamara & Houston 1996).

Discussion

In this paper we have tried to make a connection between the gene network approach and previous optimal resource allocation models and have probed the role of cell-level events during development in shaping the life histories of organisms.

Solutions found by our optimization runs have features in common with previous work in resource allocation and life history: such features are the bang-bang switch from growth to reproduction and the trade-offs between propagule size and time of development to maturity and between propagule size and number. An advantage of our approach in comparison with previous work is that, through the use of lower level state variables, our model encompasses many life history characters in a natural way; for instance, in our model the form of fecundity as a function of age, organism size or reserves, falls out naturally from the underlying physiology of cell differentiation. In previous work relations between fecundity, survival, size, surplus energy and so on have been based upon reasonable assumptions but differ substantially across models; it is not always clear what these differences imply or how they map to real physiological processes in an organism. Our model goes some way towards addressing this problem.

Our approach has additionally provided a reductionist window into the lower level workings of the solutions: it has, for instance, revealed the phenotypic convergence of solutions that differ in their low level parameters, the importance of regulating tightly gene product concentrations in propagules, and the correlation of propagule size, a cell-level feature, to the two kinds of phenotypes observed in our solutions.

Finally, as was mentioned in the Results, our life history solutions can respond to certain features of the selective environment, like the presence of intrinsic mortality, but cannot adapt to others, like increases in the level of extrinsic mortality. This may be due to constraints imposed by the number of genes and other parameters, as well as the genotypic structure of the model, and can be viewed as an illustration of the phylogenetic constraints within which selection has to move in order to optimize life histories; with the fixation of traits within lineages and other such lineage specific effects some the-

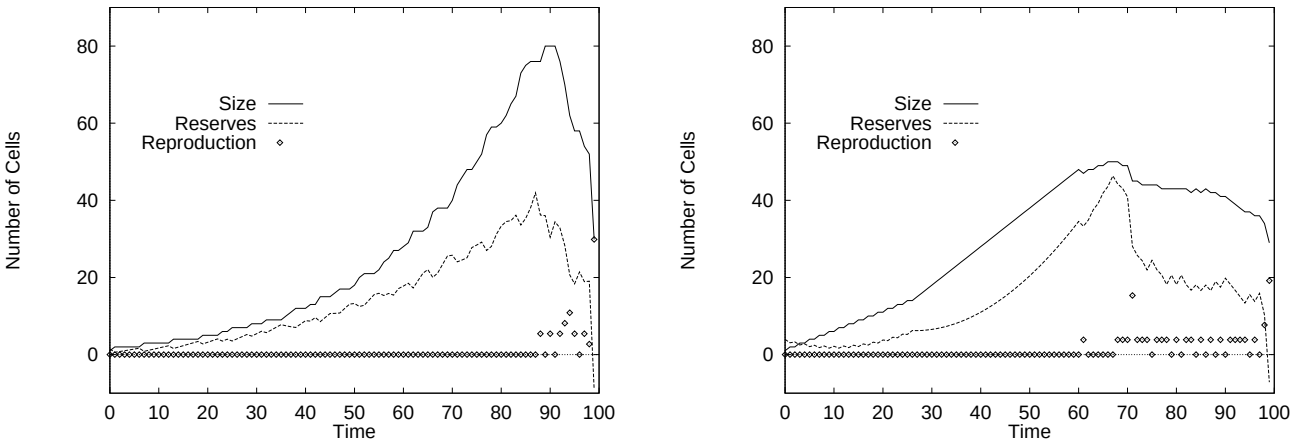

Figure 2: Solutions obtained by optimization fall into two life-history phenotypes: (A) older age at maturity and smaller propagule size, and (B) earlier age at maturity and larger propagule size. Illustrations (A) and (B) in this figure correspond to solution 1 for $\mu_e = 0.010$ and solution 2 for $\mu_e = 0.017$ of Table 1, respectively. Organism size, amount of reserves and reproductive effort (i.e. number of propagules produced times propagule size) are plotted against time (age); all three quantities are measured in the same currency used in the model, namely number of cells (see text for more details).

oretical optima may not be reachable.

Acknowledgements

Supported in part by the Yale Institute for Biospheric Studies (Center for Computational Ecology), and the Yale Center for Parallel Supercomputing, and by an Office of Naval Research grant (number N00014-97-1-0422).

References

Blarer, A., and Doebeli, M. 1996. Heuristic optimization of the general life history problem: A novel approach. *Evolutionary Ecology* 10:81–96.

Cohen, D. 1971. Maximizing final yield when growth is limited by time or by limiting resources. *Journal of Theoretical Biology* 12:19–29.

Gadgil, M., and Bossert, W. 1970. Life historical consequences of natural selection. *American Naturalist* 104:1–24.

King, D., and Roughgarden, J. 1982. Graded allocation between vegetative and reproductive growth for annual plants in growing seasons of random lengths. *Theoretical Population Biology* 22:1–16.

Kozłowski, J., and Wiegert, R. G. 1987. Optimal age and size at maturity in annuals and perennials with determinate growth. *Evolutionary Ecology* 1:231–244.

Kozłowski, J. 1992. Optimal allocation of resources to growth and reproduction: Implications for age and size at maturity. *Trends in Ecology and Evolution* 7:15–19.

Marnellos, G., and Mjolsness, E. 1998. A model of optimal resource allocation to growth and reproduction using gene networks. Technical Report CS97-568, Computer Science and Engineering, UCSD.

Marnellos, G. 1997. *Gene Network Models Applied to Questions in Development and Evolution.* Ph.D. Dissertation, Yale University.

McNamara, J., and Houston, A. 1996. State-dependent life histories. *Nature* 380:215–221.

Mjolsness, E.; Garrett, C.; Reinitz, J.; and Sharp, D. 1995. Modeling the connection between development and evolution: Preliminary report. In Banzhaf, W., and Eeckman, F., eds., *Evolution and Biocomputation, Computational Models of Evolution*, volume 899 of *Lecture Notes in Computer Science*. Berlin: Springer. 429–453.

Mjolsness, E.; Sharp, D.; and Reinitz, J. 1991. A connectionist model of development. *Journal of Theoretical Biology* 152:429–453.

Perrin, N., and Sibly, R. 1993. Dynamic models of energy allocation and investment. *Annual Review of Ecology and Systematics* 24:379–410.

Roff, D. 1992. *The Evolution of Life Histories.* New York: Chapman and Hall.

Stearns, S. 1992. *The Evolution of Life Histories.* Oxford: Oxford University Press.

Vincent, T., and Pulliam, H. 1980. Evolution of life history strategies for an asexual annual plant model. *Theoretical Population Biology* 17:215–231.