Chapter 1: Introduction

In response to changes in the environment and physiology, organisms can shift metabolism, switch developmental programs, modulate behavior, or change shape and size, leading to a distribution of phenotypes or phenotypic plasticity (Brockmann, 2001). Phenotypic plasticity can arise from genetic or environmental forces, reshaping populations and diversifying species. Plasticity arising from genetic differences is known as polymorphism and when rare (under 5% penetrance) as a mutation. Plasticity arising from environmental conditions is known as a reaction norm which is characterized by a range of phenotypes, and polyphenism when there are only 2 phenotypes (Gilbert, 2009).

In some cases, polyphenisms entail a binary decision between two mutually exclusive outcomes (Braendle et al., 2008). Such decisions involve three main phases: (i) measurement and integration, in which both environmental conditions and internal states are measured and integrated into a decision; (ii) commitment, in which a change of environmental conditions or cues does not change the result of the decision and (iii) signaling and implementation, in which a set of molecular and cellular processes drive the decision thus dispersing it throughout the responding cells/organs. Decisions in these cases are often irreversible and thus represent commitments to different fates. I will discuss the challenges that this type decision making system must overcome in the nematode *C. elegans* and generalize by providing similar examples in other organisms.

Types of environmental conditions cues and assaults

Organisms can survive and reproduce in a wide range of environments composed of often multiple and different physiochemical compounds food sources stresses and assaults. Organisms will maximize fitness by selecting a habitat that can offer them the best protection from predators, low competition or abundance of food and nutrition sources and a selection of mating partners. Environments can also be unpredictable to some organisms but predictable to others therefore, an organism that can predict its environment has a higher fitness. In fact, observational and theoretical work in the field of sociobiology have defined two main types of strategies that organisms employ in order to maximize their fitness in an environment, known as r and K selection theory. An r strategist is a species that typically lives in a niche that is subjected to random fluctuations in environmental conditions with resources far from exhaustion. It will survive well if it can use its resources faster than the competition, reproduce quickly and disperse efficiently before a catastrophe hits the niche. These strategists usually have a short life cycle, are quick to reproduce in large numbers and do not rear their broods. On the other hand, ‘K strategists’ are those that will live in niches that are less random, resources are closer to exhaustion. Therefore, a K strategist will tend to have a longer life span, will have a smaller brood which it will rear and be a specialist in extracting resources from the environment (Wilson, 2000). These strategies are abstractions and represent the idealizations in these types of behaviors, and in reality organisms will classify somewhere between these extremes. This thesis will not deal with sociobiology, sociobiology-theory, nor evolutionary theory, but I will use these terms to lay a framework for the development mechanism that maximize fitness in uncertain and heterogeneous (complex) environments. The importance of r and K strategists will

become clear in the 2nd chapter when I will discuss the critical period, or the integration period during which *C. elegans* integrate food availability, population density and temperature in order to determine what polyphenic trait they will adopt. Phenotypic plasticity is an important adaptation to environmental conditions and while some adaptations may be the result of a physiochemical interaction with a reagent in the environment, polyphenism is a regulated form of adaptation and the forces that shape its regulation and implementation have been selected for in evolution. In my view, polyphenism is a collection of mechanisms or a sub-strategy that can implement or execute the strategy selected by evolution. It is worth therefore to explain the current use of the term and where its definition falls within the context of phenotypic plasticity.

Phenotypic plasticity and polyphenism

Phenotypic plasticity can arise from genetic or environmental forces, reshaping populations and diversifying species. Plasticity arising from genetic differences is known as polymorphism and when rare (under 5% penetrance) as a mutation. Plasticity arising from environmental conditions is known as a reaction norm which is characterized by a range of phenotypes, and polyphenism, when there are only two phenotypes (Gilbert, 2009). For example, the locust *Scistocerca gregaria* morphology is regulated by population density; in low population density they develop into a green morph with short wings and a high population density into a dark morph with larger wings (Tawfik et al., 1999b). Queen formation in the honey bee, *Apis mellifera*, is dependent on a 'royal jelly' a protein-rich food secreted by other workers. If a bee is fed 'royal jelly' for most of its larval life it will develop into a queen otherwise into a worker bee (Rachinsky et al., 1990).

One of the most intriguing aspects observed in polyphenisms across different multi-cellular species is that the inducing environment is different than the selective environment, i.e. the environment that the specific morph is selected for (Nijhout, 2003). For example, the butterfly *Bycyclus anynana* has two wing morphs, a spring bright orange morph and a summer black-white morph adapted to provide camouflage. The induction of both morphs happens in the preceding months (due to a change in photoperiod) before the actual season has begun (Beldade et al., 2002). The inducing environment in itself does not constitute a threat, danger or unfavorable environmental condition, but it usually serves as a predictor for one. Therefore, there usually is a lag between the critical period in the inducing environment to the onset of the favored morph of the selective environment. The lag between the critical period and the morphological change is the time required to initiate the changes necessary for the favored morph, suggesting that an event or set of events during the critical period has a strong correlation with the morphology selected (Nijhout, 2003).

Sensation measurement and response to environmental conditions

The correlation between the inducing period and the selection period does not hold true in single cell organisms such as bacteria and yeast. The bacteria *Bacillus subtilis* responds to starvation and high population density by testing out many developmental alternatives such as increasing motility and competence before committing to sporulation (Stephens, 1998). The *Streptomyces* species sporulate when developing in a starved or fluctuating environment (Chater, 1993).

Organisms have developed several responses to random fluctuation or uncertain environmental conditions. For example, the yeast *S. cerevisiae* is the impulse response to fluctuating environmental conditions. Upon environmental perturbation such as brief heat shock or osmotic stress that does not illicit a specific stress response ~900 genes are regulated in order to return the cell to the previous state (Chechik and Koller, 2009). Random fluctuations in food or other environmental cues which illicit a transcriptionally dependent response are often assessed over a period of time to see if they are real. This type of sensing mechanism is called a persistence detection and will filter out signals of too short a duration and is found in the L-arabinose transcriptional response in *E.coli* (Alon, 2007). Another type of response to random fluctuations is hedge betting, where random cells in a population will initiate gene expression and others will not, increasing the odds of the population as a whole to adapt to the environment (Veening et al., 2008). Most of characterized molecular mechanisms that deal with fluctuating or unpredictable environmental conditions have been performed in single cellular organisms or mammalian cell cultures (Yosef and Regev, 2011) and little is known about molecular mechanisms that regulate uncertain conditions in multi-cellular organisms. The stability or fluctuation of environmental conditions is a relative term; a single cell will sense random changes in the environment on a short timescale while a multi-cellular organism will detect changes on short and long timescales. The gut and epidermis developed in multi-cellular organism, buffer against fluctuations from the environment and create a homeostatic internal environment and therefore are less susceptible to random fluctuations in environmental conditions. Nonetheless, multi-cellular organisms have a longer life span and respond to fluctuations in temperature

(seasons) food and predators (predator-prey cycles), wet and dry seasons etc. Additionally, they have an internal environment which can be targeted by pathogens and therefore the immune system has evolved to face those challenges.

Environmental measurement and integration in multicellular organisms

Organisms adapt to the environment be it biotic or a-biotic, stable or volatile, but how are the environmental cues interpreted in the organisms to elicit a morphological change? The molecular mechanisms that orchestrate the complexity of polyphenism, have been mapped three main categories of responses (Gilbert, 2005). (i) Direct transcriptional regulation, such as a diet effects on methylation patterns (Waterland and Jirtle, 2004). (ii) Direct interaction of an environmental reagent with signal transduction cascades can regulate gene expression. (iii) Effects through the neuroendocrine system. This thesis will concentrate on mechanisms that fall into the latter category.

Neuroendocrine regulation of polyphenism

The communication of environmental cues the body followed by a morphological adaptation have been explored in many organisms and several themes and recurring regulation patterns have emerged. In multi cellular organisms, neurons detect and measure cues (and in the critical period, specific cues that may predict unfavorable conditions) chemicals pheromones, kairomones and mechanical stress from the environment. These measurements are integrated with the information of the internal state of the organism such as fat storages, intact chromosome structure, hormone availability. The neuroendocrine system then signals the rest of the body the proper

physiological response by secreting the relevant hormones. Many environmental conditions are signaled through hormonal regulatory networks and specific environmental cues have elicited conserved hormonal responses as a way to coordinate morphology between tissues. For example, the release of Juvenile Hormone (JH) in hymenopterans (ants, bees, beetles) is a result of high food intake during development which will lead to a queen or a worker (bees) or induce growth of large horns in the dung beetle *Onthophagus taurus* (Emlen and Nijhout, 1999). Polyphenisms that emerge as a function of temperature are regulated by Ecdysone in insects (Nijhout, 2003) and population density is regulated by Corazonin (insects) and glucocorticoid stress hormone in fish (Gilbert, 2009). During development there is a sensitive period of hormonal activity in which it exudes an effect. Addition of hormone during the sensitive period will elicit a future response during the selective period, but will have no effect on the morphology if administered before or after (Nijhout, 2003). For example, exogenous addition of the JH hormone to ants (*M. rubra)* at the sensitive period during development delays metamorphosis leading these ants to grow in size and develop into a queen. Addition of JH after metamorphosis or before the sensitive period results in worker or soldier ants (Brian, 1974).

Hormonal regulation mechanisms

Hormones can act through the neuroendocrine system having systemic effects (Nijhout, 2003). Hormones can diffuse through membranes and act in cells by two main mechanisms; (i) binding to internal nuclear hormone receptors, or (ii) through direct binding to GPCRs in the membrane-mediated steroid signaling pathway (Denver, 2007).

Nuclear hormone receptors (NHR) usually have modular domains such as a ligand binding domain which binds the hormone and a DNA binding domain which recognizes and can bind to specific sequences in the genome. NHRs are usually inactive until they bind the hormone and often homodimerize or heterodimerize when the hormone diffuses into the cell. Thus, the activity of hormones is extremely modular and can be regulated by alternative splicing, cell and tissue specific and temporal transcription of the NHRs, their combination in target tissues and the state of the genome; if the DNA binding sequence is accessible or held closed (Nijhout, 2003; Wollam and Antebi, 2010). Therefore, the hormone sensitive period is a function of the availability and activity of the receptors controlling a specific phenotype and not necessarily that of the hormone. The hormone can be synthesized, released or activated at any moment during the sensitive period, thus diffusing and binding to its receptors. Many types of hormone regulatory mechanisms that regulate different types of polyphenisms rely on the timing and dose of hormone secretion during the sensitive period (Keshan et al., 2006). Several examples from Nijhout (2003) are demonstrated in Figure 1.1.

Commitment to a specific fate or polyphenism

Hormones can coordinate developmental programs throughout the body, yet most traits of polyphenism are irreversible; once committed to one fate, a change in environmental conditions or an exogenous addition of the hormone triggering the specific morph will not change the decision of the morph. For example, the butterfly *Araschnia levana* will develop wing pigmentation which is bright orange in the spring and black in the summer. The summer morph is regulated by photoperiod and temperature which

triggers Ecdysone release for the summer morph alone. If these butterflies are treated with the summer inducing conditions in the spring, the wings will form the summer morph, and upon commitment, will remain the summer morph even if switched back to spring-morph inducing conditions or treated with Ecdysone (Gilbert, 2009). The Marine Goby *Trimma okinawae* can rapidly change its sex, according to specific social cues, more than once in every direction about every 4 days. Once committed to one sex they will develop into it even though the social cues for switching back are present. Irreversible decisions and commitment are recurring features in all kingdoms. Commitment is considered one of the mechanisms that canalize development and render an organism robust from environmental effects (Gibson and Wagner, 2000). Several mechanisms that determine commitment have been described in other model organisms. For example, commitment to sporulation in *B.subtilis* is controlled by a single gene, the master regulator, σ^F , which regulates expression of genes in the forespore and in the mothercell (Dworkin and Losick, 2005). Amplification and positive feedback have been shown to drive commitment in the X*enopus* oocyte. A short pulse of progesterone is necessary to start a signal transduction cascade of phosphorylation. Mos becomes phosphorylated as a result of a progesterone signal which in turn phosphorylates p42 MAPK through MEK. Positive feedback occurs when p42 MAPK phosphorylates Mos in a progesterone independent manner, forming a ‘memory module’ (Xiong and Ferrell, 2003). Interlocking feedback loops have also been implicated in locking in the 'white' or 'opaque' cell types in *Candida albicans* (Lohse and Johnson, 2010).

There is still debate if the end of the hormone sensitive period is the point of commitment, the point after which a change in environmental conditions does not change the course of development. The larvae of *Oncopeltus fasciatus* and *Pyrrhocoris apterus* treated with threshold levels of JH develop larval pigmentation on patches of their cuticle but adult surface sculpturing (Willis 1982). The metamorphosis from larvae to pupae, or Pupal commitment, in the silkworm *Bombyx mori* and the tobacco hornworm *Manduca sexta* is inhibited by JH during development ensuring that enough food has been accumulated to reach a critical mass. During the fifth instar larvae, (when nutrition is sufficient) there is an increase of the hormone 20-hydroxyecdysone, and a decrease of JH leading to pupal commitment. Addition of JH 12 or 24 hours after pupal commitment does not affect the course of metamorphosis nor does starvation (Koyama et al., 2008). The mechanism that ensures commitment to pupae is unknown.

The nematode *c. elegans* as a model organism for polyphenism

There is a large gap between our understanding of spatiotemporal regulation of polyphenism in multi cellular organisms to the detailed network architecture that explains measurement of persistent signals and commitment to a specific polyphenism or trait. The nematode *C. elegans* is an ideal organism for understanding the organismal, cellular and molecular mechanisms that regulate polyphenism. These nematodes are easily grown in laboratory conditions and amenable to facile environmental changes (Lewis, 1995). All of the cellular divisions and locations of cells during post embryonic development have been mapped extensively and easily distinguishable under high powered microscopy techniques (Sulston and White, 1980).

The *c. elegans* genome was the first multi-cellular genome to be sequenced and the first organism to enable transgenic fluorescently labeled proteins expressed within (Chalfie et al., 1994). *C.elegans* nematodes display polyphenism during development. In favorable environments, *C. elegans* develops rapidly through four larval (juvenile) stages (L1-L4) separated by molts, into a sexually reproductive adult (Figure 1.2). However, in unfavorable environments, animals can make a life cycle fate decision and develop into an alternative third larval stage, known as the dauer diapause, a developmentally arrested, long-lived form geared towards survival (Cassada and Russell, 1975; Golden and Riddle, 1984a). Accordingly, they undergo profound morphological changes including assault resistant cuticle, pharyngeal constriction and sealing of buccal cavities, which confer somatic endurance (Cassada and Russell, 1975; Golden and Riddle, 1982). Dauer larva do not feed and can endure harsh conditions, including starvation, desiccation, heat and oxidative stresses (Riddle, 1997). Whereas adult worms have a mean life span of three weeks, dauer larvae can survive for several months (Byerly et al., 1976; Cassada and Russell, 1975; Klass and Hirsh, 1976). When returned to favorable conditions, dauer larvae molt into an L4 larvae and continue into adulthood (Cassada and Russell, 1975; Klass and Hirsh, 1976).

Molecular pathways of environmental integration

The attributes of mutually exclusive fates and irreversibility imply that a fate locking mechanism underlies dauer formation, yet the cellular and molecular basis of this binary decision is not entirely clear. Environmental cues are detected by sensory neurons, namely ASI, ADF, ASG, ASJ (Bargmann and Horvitz, 1991), ASE (Reiner et al., 2008)

and ASK (Kim et al., 2009; Schackwitz et al., 1996), which by unknown means integrate inputs into hormonal outputs. Genetic analysis of dauer formation has identified dauer constitutive (Daf-c) mutants, which form dauer larvae even in favorable conditions, and dauer defective (Daf-d) mutants, which fail to form dauer larvae even in unfavorable conditions (Albert and Riddle, 1988; Riddle, 1997). Molecular dissection of these loci reveals at least four signaling pathways. Components of neurosensory structure and guanylyl cyclase signaling are involved in sensing temperature, nutritional cues and dauer pheromone (Birnby et al., 2000), which are integrated by Insulin/Insulin-like growth factor (IIS) and TGFβ signaling. These peptide hormone pathways converge on a steroid hormone pathway, which metabolizes dietary cholesterol into several bile acid-like steroids, called the dafachronic acids (DA) (Gerisch and Antebi, 2004; Gerisch et al., 2007; Gerisch et al., 2001; Jia et al., 2002; Mak and Ruvkun, 2004; Motola et al., 2006; Rottiers and Antebi, 2006). DAs serve as hormonal ligands for the nuclear hormone receptor transcription factor DAF-12, which regulates the life cycle fate decision (Gerisch et al., 2007; Hannich et al., 2009; Motola et al., 2006; Patel et al., 2008; Rottiers and Antebi, 2006). Notably, liganded DAF-12 promotes reproductive development (Gerisch and Antebi, 2004; Mak and Ruvkun, 2004; Motola et al., 2006), whereas unliganded DAF-12 together with the co-repressor DIN-1S direct the dauer fate (Gerisch et al., 2007; Ludewig et al., 2004; Motola et al., 2006). Thus DAF-12 serves as the switch between reproductive and dauer modes.

The cytochrome P450, DAF-9, works as the last enzyme in the pathway of DA production and is a critical player in the dauer decision. *daf-9* is expressed in two neuroendocrine cells namely XXXL and XXXR from hatch into adulthood, in the

hypodermal syncytium from mid-L2 to L4 stages (but not during the dauer stage), and in the adult spermatheca (Gerisch et al., 2001; Jia et al., 2002). Consistent with a hormonal mechanism, DAF-9 works cell non-autonomously to control dauer formation (Gerisch and Antebi, 2004; Mak and Ruvkun, 2004). By contrast, *daf-12* is widely expressed in most tissues and throughout development (Antebi et al., 1998; Antebi et al., 2000). With respect to dauer phenotypes, *daf-12* null mutants (Daf-d) are epistatic to *daf-9* null mutants (Daf-c, Gerisch et al., 2001; Jia et al., 2002), yet hypodermal expression of *daf-9* is DAF-12 dependent, suggesting that a feedback loop upregulates hypodermal *daf-9* expression in response to upstream inputs (Gerisch and Antebi, 2004; Mak and Ruvkun, 2004).

The molecular and cellular basis comprising the binary nature of the life cycle fate decision remains elusive. It is unknown whether DAs are secreted as a result of a decision or as a means for integrating multiple environmental stimuli and genetic inputs controlling the decision. In chapter 2, I describe the effects of population density signal strength, duration and fluctuation on the decision to become dauer. In Chapter 3, I describe the hormone sensitive period of DA and demonstrate that they can act as a diffusible messenger downstream of the decision. I show that high amounts of DA are necessary to coordinate the reproductive growth fate decision throughout the whole animal. In chapter 4, I demonstrate how the amplification of DA in the hypodermis is responsible for the irreversibility of the decision. I propose that hypodermal amplification acts as a fate locking mechanism that enforces the binary decision.

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Figures

Figure 1.1

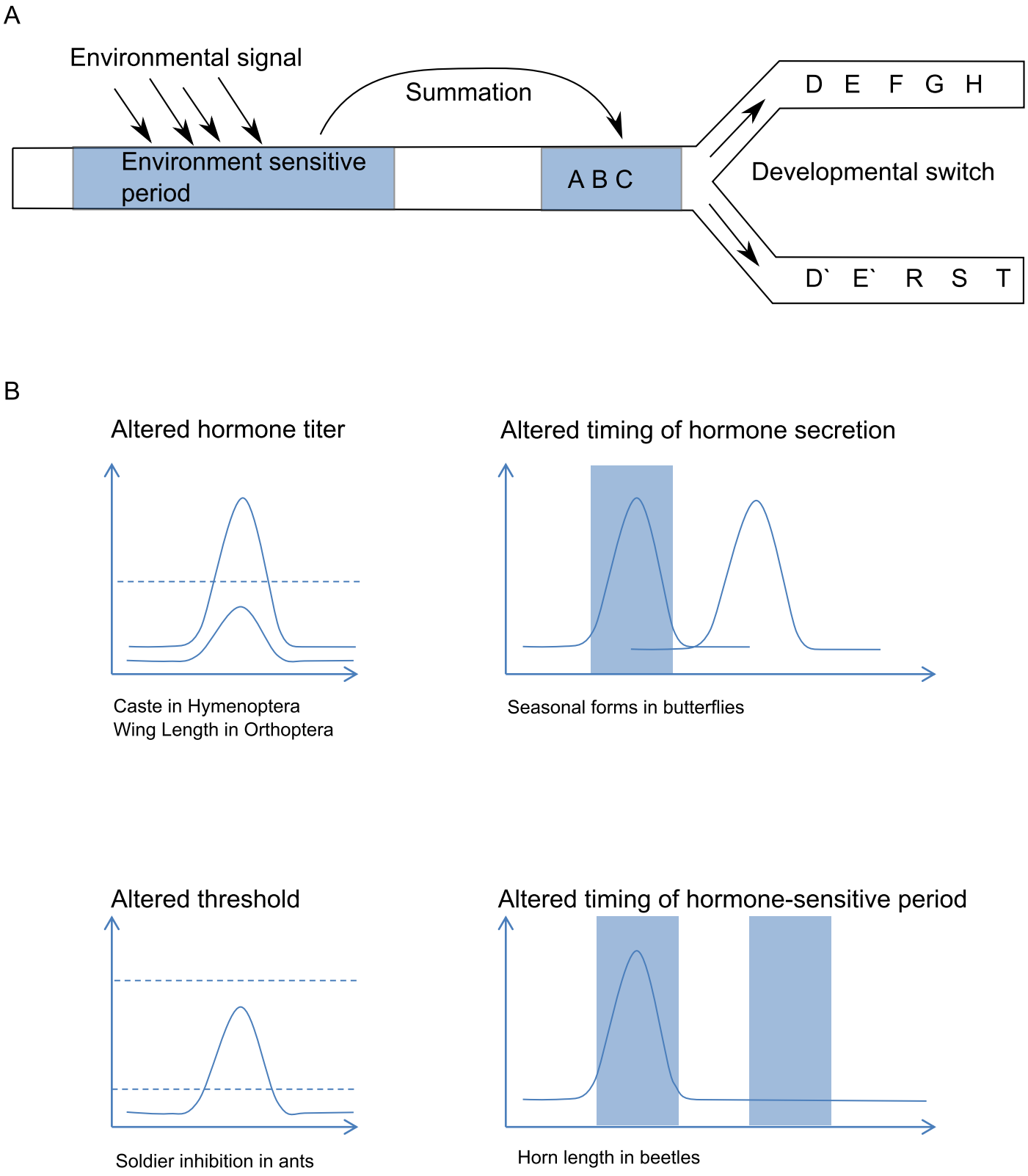
A
Environmental signal
Summation
Environment sensitive period
A B C
D E F G H
Developmental switch
D` E` R S T
B
Altered hormone titer
Caste in Hymenoptera
Wing Length in Orthoptera
Altered timing of hormone secretion
Seasonal forms in butterflies
Altered threshold
Soldier inhibition in ants
Altered timing of hormone-sensitive period
Horn length in beetles

Figure 1.1: Endocrine mechanisms underlying the polyphenic switch in insects

Adapted from Nijhout (2003): (A) Diagram of development and rise of polyphenism: Environment sensitive period is when insects measure and integrate environmental conditions and cues. The results of the integration or summation are manifested in the developmental switch where hormonal regulation mechanisms carry out the programs that give rise to the selected morph. (B): Examples of four developmental switch types that have been identified in insects. In all cases, the hormones act in the hormone-sensitive period, which is presumably dictated by the tissue specific availability of the relevant nuclear hormone receptor. The two morphs that compose the polyphenism are a function of hormone titer being above or below a threshold value during the hormone sensitive period.

Figure 1.2

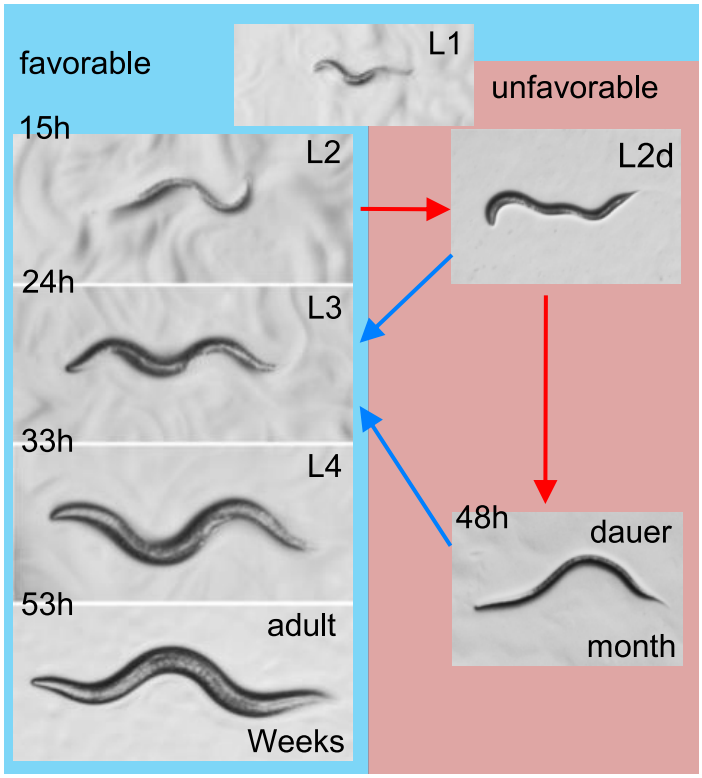
favorable
L1
unfavorable
15h
L2
L2d
24h
L3
33h
L4
48h
dauer
53h
adult
month
Weeks

Figure 1.2: Developmental molt times of *C. elegans* wild-type strain

Developmental molt times of wild type, N2 *C.* elegans larvae growing in favorable (blue) or unfavorable (red) conditions. L2d's exposed to favorable conditions before committing to the dauer fate can resume development through the L3 stage to adulthood (see chapter 1 for details). Dauers exposed to favorable conditions can resume development through the 4th larval stage and growth to reproductive adulthood.