Modelling fish growth under hormonal regulation as a factor in Pace of Life

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Abstract

This thesis is written with the aim to increase the holistic understanding of growth in fish. As stated by Tinbergen (1963), to fully understand a behaviour or trait one needs to understand several perspectives of it. Those perspectives cover proximate causes, as ontogeny and mechanisms, and ultimate causes, as phylogeny and function. Empirical studies often acquire new knowledge about a trait within the boundaries of one of those perspectives. Thus, they clearly belong to one distinct biological discipline. This is the case for purely physiological studies explaining how a certain trait or behaviour is realized in an organism, as for example the colouration of fins by metabolic carotenoids (Eckmann et al., 2017). Thereby they answer one of Tinbergen's questions, in this case a mechanism. It is also the case for studies on purely evolutionary questions as for example whether fin coloration increases a male's mating success (Kuwamura et al., 2000). Here, the ultimate causes of behaviour are explained.

Even if Tinbergen's four question have been summarized into two main topics; the proximate "how come" and the ultimate "what for", as by Dennett (2017), there is still a gap separating the perspectives.

About two decades after Tinbergen, Grafen (1984) nicknamed the dominant methodological tactic in evolutionary ecology for studying ultimate explanations "the phenotypic gambit". Thus he criticized the then (and now) still common practise among evolutionary ecologists to overlook two of Tinbergen's four questions, thereby assuming that ultimate mechanisms will serve the organism's demands to reach evolutionary goals without any constraints. This assumption has been necessary for many evolutionary studies in which physiological explanations are inaccessible or would complicate the study design a lot. At the same time those studies take a greater distance from Tinbergen's and later Dennett's call for a holistic understanding.

While the phenotypic gambit reduces the complexity of a trait's cause to a primarily ultimate explanation, the opposite is the fact for pace-of-life syndromes (POLS). Having their origin in the *r*-/*K*-selection (Pianka, 1970), and later slow-fast continuums (Gaillard et al., 1989), POLS has been an extending concept now including both physiological, behavioural and ecological (Ricklefs and Wikelski, 2002, Martin Ii et al., 2006, Reale et al., 2010, Careau and Garland, 2012) factors. Slow-fast continuums build upon a suite of life history traits that change in a related manner. Individuals in species at the slow end have shorter lifespans and juvenile phase, lower survival but mature early and are highly fertile (Gaillard et al., 1989, Oli, 2004, Jeschke and Kokko, 2009). The further development of slow-fast continuums to POLS and inclusion of physiological traits, combines the ultimate life history of individuals with its proximate mechanisms. Studies show such POLSs occurring at inter-(Sepp et al., 2018) and intraspecific (Binder et al., 2016) levels.

Here, I chose to follow Tinbergen in combining knowledge from distinct biological diciplines to get a better understanding of fish growth. Using a state-dependent optimazition model, the model structure allows for building a complex inner architecture of the model organism, including bioenergetics and endocrinal regulation. At the same time, decisions made by the model organisms are based on their life histories.

This thesis focuses on the development of an optimization model for fish growth (**Paper I & II**). The model is meant to be a working tool, which can be tailored to different ecological and evolutionary questions, as shown for mortality in **Paper III**. The main emphasis of our work was to simplify the endocrinal system related to growth in the juvenile phase of fish (**Paper I**). By defining three hormone functions based on growth hormone, orexin and thyroid hormone, respectively, we designed the endocrinal system of the model organism. This system regulates growth, foraging activity and metabolism. A second important step was the implementation of the fish metabolism, here, in form of "by-demand bioenergetics". This goal-driven control system supports individual growth with energy from foraging under the constant

regulation of the endocrinal system. Parametrization was based on empirical studies on Atlantic cod, when available. If not, other studies close to cod were preferred. Concerning environmental influence on the organism we decided to focus on mortality. Model organisms can experience mortality from different sources, like foraging-related mortality or by gape-limited predators. Strategies emerging from the model are validated with empirical data.

As the first paper (**Paper I**) mainly concerns internal aspects of the model organism, the second paper (**Paper II**) focuses on the environment. By advancing from a static food environment, as used in the first paper, to a stochastic food environment, simulations allow for individual differences. Stochasticity is based on an auto correlated process.

In the third chapter of this dissertation (**Paper III**) I use the optimization model developed in the two previous chapters in an ecological context of different predation profiles. By defining a gradient along which total mortality remains approximately constant, I study the effect of mortality classes weighted differently against each other. The two mortality classes used are defined as strategy-independent, including gape-limited predation, and strategy-dependent, like foraging-related mortality. Faster pace-of-life syndromes are seen when the proportion of strategy-independent mortality increases. Thus, shortening the juvenile phase through higher endocrinally provoked growth rates. From model results we can suggest that differing predation pressures are able to result in intraspecific diversification.

Although there is still much unknown territory between genes and behaviour, this thesis with its three papers shows that the ultimate evolutionary perspective can be used in combination with mechanistic understanding of molecular dynamics to reduce the size of the phenotypic gambit.

List of Papers

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Additional Paper:

Jensen, C. H., Weidner, J., Mennerat, A., Giske, J., Jørgensen, C. & Eliassen, S. (manuscript). Apparent manipulation: How parasites may modify their host`s behaviour without using any tricks.

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1. Introduction

1.1 Reductionist views in biology and their value for holistic explanations

To understand a certain process a biologist often has to go into detail. To understand an organ, one can study single functions, cell types or metabolic pathways. To understand an ecological relationship, one can set up an experiment or build a theoretical model in which one or a few factors vary, and everything else is held constant. Having several such detailed studies one can put them together, to understand the organ or ecological relation. The more detailed the studies are, the more robust the explanation should be. Dividing a complex system into smaller and smaller pieces, which can be understood one by one, is called methodological reductionism (Fang and Casadevall, 2011). Reductionism in biology is essential for scientists as most things are too complex to accomplish explanations by single studies. It is widespread in today's biology (Marler, 2005). Reducing a complex system into many small bricks also helps in other natural sciences as physics and chemistry. By studying different materials their structure has been described from being build up by molecules, ions, atoms, subatomic particles like protons and even quarks and gluons. Even if all three natural sciences go into detail to understand, there is a fundamental difference between how those bricks are understood. While physicist and chemists can consider their bricks as entities, which can be described without references to other parts of the system, a biologist always has to refer to the system the brick is part of. While the existence of an entity in physics and chemistry can be understood from its components and the forces operating on the entity, a biological entity must also be understood from its contribution to the evolutionary stability of the organism and gene pool it is part of. Thus, biological entities can be studied both from a bottom-up and a top-down perspective.

Different biological disciplines have emerged because understanding of a biological system depends on understanding the details of it with ever greater precision. Each

discipline contributes with its own methods, assumptions and goals. Thus, several disciplines can study one trait, but from different points of view.

The advantage of studying a trait within the concepts and methods of a certain discipline, while ignoring others, is also used by evolutionary biologists and ecologists. The methodological tactic is referred to as the phenotypic gambit (Grafen, 1984). Its name is based on a chess opening in which a player, in order to develop a valuable piece, sacrifices a less valueable piece (Schiller, 2002). For an evolutionary biologist working on individual traits, this would mean to sacrifice knowledge about genetics of the individual. Instead the biologist assumes that the genotype gives the individual an unbounded phenotypic flexibility, so that the researcher can answer questions about the evolutionary cause of traits and behaviours without considering details of mechanism. It follows from this assumption that selection pressure directly influences the evolution of behaviour (Garland et al., 2016). Yet, researchers in this tradition are well aware that ignoring mechanisms may lead to erroneous conclusions (e.g. (Fawcett et al., 2013, Higginson et al., 2018)). But they can also point at great achivements obtained by simplification, such as the Optimal Foraging Theory (Schoener, 1971, Pyke, 1984). The core of this thesis is to investigate effects of combining bottom-up and top-down forcing.

How to combine different ways of understanding has been discussed many times, among others by Mayr (Mayr, 1961) and Tinbergen (Tinbergen, 1963). According to Mayr, the questions that should be asked to clarify the proximate and ultimate causes of trait maintenance are “how” and “why” respectively. By studying both levels of analysis, non-overlapping and mutually supportive explanations are found (MacDougall-Shackleton, 2011).

Two years after Mayr’s publication, the well-known and often cited paper of Tinbergen (Tinbergen, 1963) was published. He broadened the explanation horizon by introducing four questions focusing on proximate properties of behaviour like ontogeny and mechanism and ultimate properties like phylogeny and adaptation.

Studying a behaviour by answering several of those four questions is one of the first steps towards a holistic explanation. Here, a holistic explanation combines explanantions from several separate aspects, which in combination reveal a better insight than the pure sum of them. However, the real benefit of combining the knowledge lies in the links that emerge from constraints and possibilities given by one discipline and used by another (McNamara and Houston, 2009, Higginson et al., 2018, Frankenhuis et al., 2019).

The philosopher Daniel Dennett summarized Tinbergen's four questions again into two main questions, asking for the proximate and ultimate causation of a behaviour (Dennett, 2017). However, the words he chose to phrase his questions were different from those of Mayr. While Mayr used "why" for ultimate causes, Dennett used "what for". The main difference between their reasoning is the time span used when scrutinizing the ultimate causes. While Mayr focused on events in the past, Dennett focused on how the trait can be adaptive for the animal from now on, thus a shift in explanation from phylogeny to life cycle completion. The logic of asking for future evolutionary benefits lies in the assumption that each new generation repeats the life cycle of many previous generations (Lotka, 1925). The reasoning of Dennett comes closer to our understanding of the ultimate causes in this thesis. Understanding proximate causes of a trait can identify constraints for adaptations, as organisms are not independent of their physiology when gene pools adapt to changing environments. This view is contrary to assumptions under the phenotypic gambit. Having a closer look into both levels of analysis, the proximate and the ultimate, also can lead to new hypotheses and strengthen explanations and studies (MacDougall-Shackleton, 2011).

These advantages have been recognized by scientists and the combination of disciplines has resulted in relatively new disciplines like evolutionary- and behavioural endocrinology. For the last 20 to 30 years scientists have studied perspectives not exclusively belonging to either discipline (Zera et al., 2007, Hau et al., 2008, Cox and Cox, 2020). An example is the study of the impact of insulin and

insulin-like growth factor-1 (IGF-1) on growth and reproduction in worms, flies, mice and dogs (Kenyon, 2010). By comparing individuals belonging to one species but differing in their secretion of insulin and IGF-1 or having perturbated signalling pathways for those molecules, differences in longevity, growth rate and reproduction have been observed. Any change delaying or weakening the signal resulted in increased longevity.

Thus, an endocrinal change early in life results in a shift in the life history tradjectory. In addition, behavioural endocrinology focuses on whole-animal approaches to understand the proximate fundament of complex behaviours (Marler, 2005, Cordes et al., 2014).

If the combination of disciplines yields a better understanding of a phenomenon, why do we so seldom see this done? In the case of evolutionary biology and physiology, there is a great difference in what organisational level scientists are working on, what methods they use, and the context in which they explain their results. Even more, the two disciplines are oriented towards different kinds of explanations and therefore value different types of observations. While physiology acknowledges the physical and chemical constraints on a process or phenomenon, the evolutionary ecologist will make links to fecundity, survival and natural seletion. While the top-down explanation may investigate time needed for adaptations to occur the bottom-up approach may investigate the time needed for signal transduction in synapses. Thus, while communication over discipline borders can be difficult, it may be almost philosophical between physiology and evolutionary ecology.

1.2 Endocrinology – a complex translating network

Most bodily processes in higher vertebrates are either directly regulated or in some way affected by the actions of hormones. Hormones are a diverse group of signalling molecules transported by the circulatory system (Belfiore and LeRoith, 2018). They can be sorted in three main categories – the peptide hormones, the amino acid

analouges and the steroid hormones. Their effects are seen in a great number of tissues and mechanisms as they regulate growth, metabolic pathways of energy uptake, conversion and storage of energy, reproduction and more. Amino acids and lipids, which are the building blocks of hormones, define properties of each specific hormone and affect their metabolism and their transportation in the circulatory system. Thus, the water-soluble hormones float freely in the blood stream to their target cells. This speeds up their metabolism, e.g. by the liver. Faster metabolism results in shorter half-lifes and enables the organism to change hormone signalling relatively fast. In contrast, lipid-soluble hormones bind to carrier proteins to reach their target cells. This binding affects clearance from the blood and results in longer half-lives. Insulin is an example of a short-lived hormone, while iodothyronines bind to carrier proteins and are longer-lived. The network created by hormones, when conveying messages, is extremely complex. Hormones interact with each other as well as with molecules like neurotransmitters or nutrients. The hypothalamus is a region of the brain in which signals from the neural and endocrinal system meet and interact (Belfiore and LeRoith, 2018). Some hormones even serve as translators for environmental conditions, when external factors induce hormone secretion in the organism. This is the case for melatonin, the clock hormone, in fish and mammals (Falcón et al., 2010, Rani and Kumar, 2014). The light-stimulated secretion results in melatonin concentrations translating daylength into a signal readable for internal processes. This enables individuals to prepare for changes during the day and for seasonal variation.

The complexity of hormone regulation in an organism becomes even greater when considering the network of molecules and metabolic pathways linked to a single hormone. After secretion by an endocrinal gland, e.g. the thyroid or the pituitary, a hormone depends on many other molecules to achieve its effects in target tissues (Belfiore and LeRoith, 2018). Those molecules differ between the single hormones and their actions. Some need carrier proteins, degradation proteins and receptors on target cells. As an example, thyroid hormones in mammals are secreted in a cascade,

in which triiodothyronine (T3), the biologically active form of the thyroid hormone, influences peripheral tissues, e.g. during bone growth (Zoeller et al., 2007, Waung et al., 2012). Upon internal and external stimuli, like increasing leptin concentrations or exposure to cold, the hyptothalamus secretes thyrotropin-releasing hormone (TRH) (Nillni, 2010), which is transported to the pituitary and stimulates thyroid-stimulating hormone (TSH) secretion (Zoeller et al., 2007). In a next step, TSH regulates the production and secretion of mainly thyroxine (T4), but also T3, from the thyroid gland. For activation of T4, deiodinases have to convert T4 into T3 in the liver and target tissues. The resulting T3 can bind to nuclear receptors influencing transcription, after having been transported into target cells and their nucleus. Transport of thyroid hormones in the blood is achieved by binding proteins (TBG).

Considering the network of mechanisms and molecules described above, the obvious question to ask is why we find such networks in so many taxa in nature. It might seem easier to have direct links from one external or internal stimuli, via the hormone, to the target tissue. There are three advantages of a complex endocrinal network that I want to discuss here – safety, coordinated responses, and inertia. All of them contribute to hormones being an adaptive regulatory mechanism.

Due to the pleiotropic nature of many hormones, a single hormone often affects several traits. In turn, changes in single traits are often the result of a coordinated and timed secretion of several hormones. This complex signalling network can be seen as a set of **safety** settings for endocrinal regulation. Bone growth in mammals is an example of such a fine-tuned interplay of many hormones promoting one process. Growth in humans occurs before and during puberty in growth plates, where chondrocytes develop to osteoblast. This process is under regulation of several hormones (van der Eerden et al., 2003). Growth hormone and thyroid hormones are important factors for chrondrocyte development (Robson et al., 2002, van der Eerden et al., 2003). Glucocorticoids slow down growth by altering growth hormone and thyroid signalling and access to calcium. Additionally, sex hormones like testosterone and estrogen influence growth in a promoting and inhibiting manner, respectively.

They also affect each other's production, activation and cell responsiveness. Making one process depend on signals from different organs and stimuli, reduces the chance of a sudden increase or decrease in growth rate, which is not suitable. This is also the case for other processes controlled by several hormones.

Feedback-mechanisms provide an assurance against sudden changes in hormone concentrations. They occur in single hormone axes or between different hormone systems. Such feedback-loops are found in the thyroid hormone axis (Zoeller et al., 2007). TSH exerts a negative feedback on its own production. This might also be the case for TRH. From the lower end of the axis, T4 inhibits both TSH and TRH production via feedback loops. A feedback between different hormones is known from growth hormone increasing T3 concentrations (Grunfeld et al., 1988). An effect of thyroid hormones on growth hormone is suggested, but results from studies are inconsistent (Feldt-Rasmussen, 2007).

Pleiotropic effects of hormones also shift the physiological focus of an animal, thereby causing **coordinated responses**. Assuming that growth hormone secretion is increased in an organism, this increase would lead to changes in other hormone concentrations and metabolic pathways to support growth. Thus, many physiological traits of the body change. This also implies that energy allocation to other traits, like reproduction or survival, gets smaller. In this way the interwoven hormonal network can coordinate and focus processes throughout the whole organism to proritize certain processes over others.

The same mechanism creates a form of intermediate **inertia**. One can think of an animal without hormones: then its priorities would be determined in a dialogue between life-long genetic factors and immediate sensory information. Hormone secretion keeps organisms in a certain state, e.g. homing migration, nest building, courtship, fast growth, or danger avoidance, for a period which is much shorter than life itself, but longer than a sensory signal. This is an important top-down control function of hormones (and emotions) which enables flexible re-prioritization of the

organism (e.g. Andersen et al., 2016, Budaev et al., 2019). But if the environment changes rapidly, the hormonal prioritization of the organism may not remain adequate, e.g. attempting fast growth when food availability is low. In these situations, the hormone-controlled individual may experience an undesired physiological inertia relatively to its environment, which slows down its ability to respond.

Due to the pleiotropic effects many hormones have, optimization of a hormone towards one function might inevitably result in a range of different undesired effects on other traits the same hormone regulates. Also changing the structure of a hormone cannot be accomplished without changing the structure of several other molecules, as binding proteins. Thus, additions, removals, or structural changes in the hormone system could lead to relatively wide changes throughout the endocrinal system. This could be a reason for many hormones and hormone-related proteins to be quite conserved structures, e.g. leptin receptors (Denver et al., 2011), binding sites on IGF-molecules (Niu et al., 1993) and ghrelin (Kaiya et al., 2008).

1.3 Growth and life history of fish

In fish, as in other taxa, juveniles grow from their birth or hatching to adult size. However, while many animals stop growing when maturing (Roach et al., 2003, van der Eerden et al., 2003, Woodward et al., 2011), fish continue to grow as adults (Froese and Binohlan, 2000). After maturing, they invest some of their energy into gonads and reproduction, but continue to invest in new soma. Some fish also have the ability to speed up growth after a period of slow growth, called compensatory growth (Ali et al., 2003). As smaller body sizes can be disadvantageous when it comes to reproductive success (Hutchings, 1994, Surace and Smith, 2016) and predation risk (Biro et al., 2005, Gislason et al., 2010), it can be advantageous to grow fast or eventually catch up when environmental factors allow (Jachner and Janecki, 1999, Biro et al., 2004, Biro et al., 2005).

Considering the importance of growth, a holistic understanding of drivers and constraints of fast versus slow growth is necessary. Life history traits as survival, reproduction and growth are tightly integrated processes, partly controlled by the same mechanisms. Growth can both enhance and hamper survival and reproduction.

As growth results in larger body sizes, it positively influences reproductive success. In females, egg size (Braga Goncalves et al., 2011), fecundity and total reproductive energy (Barneche et al., 2018) is related to body size. In males, body size can have an effect on paternal behaviour and the investment of fathers in their offspring (Wiegmann and Baylis, 1995). Larger male fish can also have an advantage in mate choice and produce offspring with higher growth rates (Reynolds and Gross, 1992). The large body size can also be an advantage for survival. Predators are often limited by their gape size, thus, a potential prey may benefit from having a larger body size as it reduces the risk of meeting a predator large enough to swallow it (Bachiller and Irigoien, 2013, Bystrom et al., 2015). However, there are disadvantages of higher growth rates both for survival and reproduction. Growth is an energetically expensive process and to cover the energetic demands the growing individual needs to forage. Foraging acitivity is typically assisiated with risk, as the individual must leave its hiding place and move around searching for food (Anholt et al., 1996, Krause and Godin, 1996, Skalski and Gilliam, 2002, Strobbe et al., 2011). Thereby it inceases the chance of being detected by a predator. Also, as its focus is now on food items and not predation risk, its vigilance is lowered, which also increases mortality risk (Dukas and Kamil, 2000, Budaev et al., 2019).

A trade-off in energy allocation links growth and reproduction (Fisher, 1930, Siems and Sikes, 1998, Vrtilek and Reichard, 2015). After covering energetic demands of vital functions as metabolism, a surplus of energy can be allocated to different processes, among them growth and reproduction. Thus, allocating energy to new soma hampers investing in eggs and offspring.

The regulation of growth processes and allocation of energy to growth is regulated by the endocrinal system. In fish, growth hormones and thyroid hormones play major roles in regulating growth (Robson et al., 2002, Nilsson et al., 2005). But also other hormones as insulin (Yang et al., 2018) and leptin (Won et al., 2016) take part in the physiological processes underlying building new soma.

1.4 Predation – a natural mortality factor

Predators shape life histories of species by exerting selective pressures on individuals. Despite the importance of mortality in a life history context, studies of natural mortality seem to be rare (Vetter and Vetter, 1988, Julliard et al., 2001, Gislason et al., 2010). To assess natural mortality of a species, comparisons can be made between different natural and aquaculture-related habitats (Lorenzen, 1996), based on mortality-weight relationships of juvenile and adult fish. Also capture-release-recapture studies can be carried out as for cod (Julliard et al., 2001). One reason for the scarcity of studies on natural mortality is surely the difficulty of assessing it. This lack of information entails a lack of knowledge on relations between natural mortality and other life history traits. It seems that mortality due to commercial fishing is more studied. It can for example be linked to decreases in length and age at maturity in fish (Sharpe and Hendry, 2009).

The trade-off between the fitness gain of finding food and the fitness cost of becoming food has been studied both theoretically (McNamara and Houston, 1990, McNamara and Houston, 1992, McNamara and Houston, 1994) and empirically (Holbrook and Schmitt, 1988, Allen et al., 2006). The risk of dying due to starvation or predation can be reduced by investing in fat reserves (McNamara and Houston, 1990). While high foraging rates can support high growth rates, they almost always come with increased exposure to predators. This can be detrimental in environments with high predator abundances (Biro et al., 2004) or for fish showing higher tolerances of predation risk (Johnsson and Abrahams, 1991).

While feeding usually incurs a predation risk, it may also reduce future risk. It is this trade-off between foraging and predator avoidance that can restrict individual growth (Sogard, 1997, Lima and Bednekoff, 1999, Allen et al., 2006). Effects of predation can be sublethal and impact prey individuals on decisions regarding activity, e.g. foraging (Steele and Forrester, 2002). The bigger-is-better hypothesis assumes that larger individuals of a cohort have an advantage when it comes to predation, for example due to predator's gape limitations (Miller et al., 1988, Dorner and Wagner, 2003). This may be an incentive for fast growth. Support for the hypothesis has been found for different fish populations (Sogard, 1997, Allen et al., 2006, Gislason et al., 2010). In environments with high food availability, individuals can achieve higher growth rates at lower risk and leave the critical size window quickly (Sogard, 1997). Behavioural changes to predators can be species-specific (Steele, 1998), differ with season (Steele and Forrester, 2002) and food availability (Biro et al., 2005). A high predation pressure is suggested to counteract the selection of fast-growing individuals (Biro et al., 2004).

Ecological variation in mortality regime between natural populations can select for different life histories. A classical example is the recent (in geological terms) separation of Bahamas mosquitofish (*Gambusia hubbsi*) into habiats differing in predator regimes (Langerhans et al., 2007). Here, the selective pressure from predation is suggested not only to adapt populations locally, but even to be a possible driver of ecological speciation. However, predation risk cannot directly change morphology and life history. Quite likely, the process of natural selection has involved genetic changes that have up- or down-regulated multiple hormones. One of these mechanisms is the so-called "ecology of fear" (Brown et al., 1999, Dalton and Flecker, 2014). The effect of a risking to encounter a predator can prevent an organism from using a resource (McLaren, 1974, Giske and Aksnes, 1992), where the mechanism can be genetic changes in hormones that modulate emotion systems which in turn impact behavioural decisions (Giske et al., 2013). The result of this cascade may be a change in life-history.

1.5 Pace-of-life syndromes

Ecology of fear (Brown et al., 1999), bigger-is-better (Miller et al., 1988, Dorner and Wagner, 2003), and island biogeography (MacArthur and Wilson, 1963, MacArthur and Wilson, 2001) are examples where natural selection may favour a suite of adaptations of genes impacting hormones, physiology, behaviour, and life history, shaping the individual, population, and even species. If this suite of adaptations into an integrated package of coadapted physiology, behaviour and life history can place the population into a continuum in variation in life-history from slow-lived to fast-lived lives, it is an example of a pace-of-life syndrome (POLS) (Ricklefs and Wikelski, 2002, Wikelski et al., 2003, Dammhahn et al., 2018)).

The theory of pace-of-life syndromes has its origin in *r*-/*K*-selection theory: that natural selection can lead to species adapted to ecological disturbance and high capacity for fast instantaneous rate of increase, *r,* and to species selected for competing for limited resources when the population is near the carrying capacity, *K,* of the area (Pianka, 1970). In a continuum between these two extremes, species differ in how energy is allocated between activities, somatic, and reproductive tissue. Due to the priorization of reproduction in *r*-selected species, they are more likely to be found in ecosystems characterized by low density of organisms and low competition. They invest little in each offspring, but have a great number of offsprings, thus they are characterized by high productivity. The opposite is true for *K*-selected species. Their offspring, often occuring in low numbers per reproductive event, incur high energetic costs for their parents. Individuals from *K*-selected species also are more efficient in competing for resources. In ecosystems changing from a state of low competition between organisms and low population sizes to intense competition and larger populations, a shift from dominance of *r*-selected species towards higher abundance of *K*-selected species is expected.

In the theoretical development that followed, the number of related traits was increased from the gradient given by *r*-/*K*-selection, via slow-fast continuums

(Gaillard et al., 1989), to what is now called POLS (Reale et al., 2010). Slow-fast continuums include life history traits as age at first reproduction, life expectancy, reproduction strategies (e.g. iteroparity) or morphological traits such as body weight (Gaillard et al., 1989). In the POLS concept, physiological, behavioural and life history traits are combined to suites of traits (Wolf et al., 2007, Reale et al., 2010, Polverino et al., 2018). For example is a gradient in body size (Immonen et al., 2018) linked with hormonal regulation (Jeschke and Kokko, 2009, Immonen et al., 2018) and the size of the digestive tract, metabolism and reserve use (Kieffer and Tufts, 1998, Clarke and Johnston, 1999, Immonen et al., 2018). Studies of POLS often focus on latitudinal or elevational gradients (Hille and Cooper, 2015) or correlations between traits belonging to the individual's physiology, behaviour, or life history (e.g. (Binder et al., 2016, Mell et al., 2016)), while gradients of resource availability and risk are among the lesser researched topics (Dammhahn et al., 2018).

POLS traits have been studied in a number of different species and taxa. In fish, like the Trinidadian guppy (*Poecilia reticulata*) and the mosquitofish (*Gambusia holbrooki*), and birds, lower metabolism has been found in individuals with relatively slow POLS (Hille and Cooper, 2015, Auer et al., 2018, Polverino et al., 2018). In birds, slower POLS was also characterized by slower development, decreased reproductive rates, and longer lifespans (Hille and Cooper, 2015). By comparing Eastern mosquitofish from different natural populations, fish having lower metabolic rates also were less bold and less active than fish with higher metabolic rates (Polverino et al., 2018). Similar results come from a study on Atlantic salmon (*Salmo salar*), in which more proactive fish grew and developed faster than their conspecifics having a slower POLS (Damsgård et al., 2019). POLS has been related to risks from predators and parasites. Trinidadian guppies under low predation pressure have slower metabolic rates compared to guppies living under higher predation pressure (Auer et al., 2018). Metabolism mirrors energetic expanses of the individual (Ricklefs and Wikelski, 2002, Brown et al., 2004, Glazier, 2015). Thus, a selection pressure towards higher metabolism in individuals with faster life histories, faster POLS, was

hypothesized in the study on Trinidadean guppies. Another study comparing Trinidadian guppies from populations with different predation pressure, focused on their investment in defence against parasites (Stephenson et al., 2015). As short lived-species, having a fast POLS, invest relatively much energy into reproduction and grow fast, they have less energy surplus to allocate to immune defence. For species having a slow POLS, reproduction investment is lower and immune defence stronger. Data from the studied guppy populations support the pace-of-life assumptions, as fish living under higher predation pressure and being infected had a lower condition than uninfected fish. Fish experiencing lower predation pressure seemed to be more tolerant to parasite infections. Morphological properties of mitochondria in Atlantic killifish (*Fundulus heteroclitus*) have also been related to POLS, explaining the higher respiratory capacity of fish with fast POLS (Chung et al., 2018). The importance of mitochondria for POLS emphasised by them being a main component in metabolism. Metabolism itself is discussed as a possible cause of POLS gradient, (Reale et al., 2010) but could also be a result (Ricklefs and Wikelski, 2002, Glazier, 2015, Chung et al., 2018).

A latitudinal gradient has been found for birds, with tropical birds exerting slower POLS (Hille and Cooper, 2015). This may be caused by the lack of seasonality in food availability in the tropics, but also relatively constant day length and higher disease prevalence can select for slower POLS. A latitudinal gradient is also reported for Atlantic killifish, probably driven by temperature differences (Chung et al., 2018).

Glucocorticoids, which are steroid hormones, are important for decisions on energy allocation, reproductive investment and energy use in stressing situations (Casagrande et al., 2018, Immonen et al., 2018). In birds, baseline glucocorticoid levels have been related to reproductive investment and clutch size due to their energy-mobilizing effect (Casagrande et al., 2018). Also, insulin-like growth factor 1 (IGF-1) has been suggested as one underlying cause of POLS. As a hormone with pleiotrophic effects, amongst others on growth, its secretion depends in part on nutrient availability (Immonen et al., 2018). For passerines, IGF-1 could be an

important factor for life history and POLS as higher levels result in increased body size, but also decreased lifespan (Lodjak et al., 2018). Additionally, the melanocortin system, sex steroids, and non-hormone signalling molecules like dopamine have been suggested to play a role in underlying mechanisms of POLS (Immonen et al., 2018).

There are also studies failing to find POLSs. In their meta-analysis, Royaute et al. (2018) found little overall support for the POLS concept. Three reasons for the lack of support were discussed; violation of POLS assumptions in several studies, differing methods in behavioural studies, and the role of the individual`s environment in maintaining POL syndromes (Montiglio et al., 2018, Royaute et al., 2018, Salzman et al., 2018). An important POLS assumption is based on the allocation of energy under limited resource availability. Animals experiencing abundant resources can allocate energy freely to increase growth or lower mortality risk. This can be the case in experiments, but conditions like this will suppress POLS (Ricklefs and Wikelski, 2002, Reale et al., 2010, Montiglio et al., 2018). Environmental factors can play a major role in changing individual traits and shaping correlations between them. Evironments should therefor be taken into account when studying correlated traits as done in POLS (Reale et al., 2010, Royaute et al., 2018). Besides, POLS might not be an appropriate framework for predicting correlated changes in behaviour, physiology and life history. Since environment can be a maintaining factor for POLS and many of the POLS traits are difficult to measure in the field, theoretical studies of correlations gain importance.

A recent review on POLS (Dammhahn et al., 2018) calls for more interdisciplinary work between theoreticians and empiricists. They argue that there is a scarcity of theoretical models that could contribute to build empirically testable hypotheses. This is especially the case for models including ecological factors. Although ecology and environment are given as drivers for POLS, these factors are overseen in many studies. They also call for theoretical studies of POLS at different hierarchical levels, like the gene-, organismal-, population- and species level.

1.6 Aims and scope

The overall **aim** of this thesis is to contribute to narrowing the gap between proximate and ultimate explanations for growth in juvenile fish. Therefore, the work method has been to develop and thereafter investigate a model for top-down evolutionary optimization at a level where bottom-up mechanistic explanations dominate. The hormone system involved in regulation of growth in juvenile fish was therefore chosen as the **scope** for the thesis work.

Three specific aims follow from this choice of overall aim and scope:

1. Develop a comprehensive but at the same time as simple as possible model of hormonal control of growth in juvenile fish (**Paper I**)
2. Investigate whether this model can be used to study adaptive control of the phenotype, and investigate whether optimization at an intermediate level can improve our understanding of the phenotype relative to optimization of behaviour (**Papers I – II**)
3. Investigate whether concerted hormonal control can explain integrated organismic syndroms involving physiology, behaviour and life history (**Paper III**)

2. Methods

All three papers in the thesis use a state-dependent optimization model (Mangel and Clark, 1988, Houston and McNamara, 1999). This is a much used method in evolutionary ecology but also in many other fields (e.g. economics: (Sohngen et al., 1999); engineering: (Lin et al., 2003); environmental sciences: (Riaz et al., 2013); management: (Rusmevichientong et al., 2010)) to find solution in cases where the optimal choice depends on some kind of state of the agent. In evolutionary ecology the state will typically be related to the physiological condition of the animal.

The ultimate characteristic of a state-dependent optimization model is to find the optimal policy for each state/time combination by backwards iteration time-step by time-step from all possible states at the end of the final time step. This procedure is called backwards induction and is much cheaper in terms of computation demands than to try to estimate the exponentially expanding room of possible future states if the calculation should start at the beginning of the first time step.

Some state-dependent optimization models stop here, while other models use the optimal policy found in the backwards induction in a next step: a forwards iteration of individuals from the beginning of the first time-step. These individuals will follow the optimal policy for each state/time combination they arrive in, but chance effects can spread a population of such individuals into states with different optimal policies.

We have used both these steps to study optimal hormonal regulation of growth and metabolism in fish and the following population consequences. The model combines information from empirical studies on how organisms function and interact in nature. Used as “thinking aids” (Kokko, 2007), the model can be used to test our understanding of mechanisms and relationships in nature. As models are simplified versions of individuals and environments, they also force us to focus on a few aspects and sort out factors of minor importance. To test our model prediction, empirical testing and validation is necessary.

By using an optimization model, we search for an evolutionary endpoint in a given environmental setting. This means that the method will find the strategy that will maximize Darwinian fitness on the premises of the factors specified in the model, but the method will not investigate how easy or hard it is for evolution by mutations and natural selection to find this solution.

We simulate individual trajectories over time where multiple decisions about energy allocation and investment in growth and reserves have to be taken. Each decision depends on the individual's current state and will have an impact on available options in the future (Houston and McNamara, 1999, Clark and Mangel, 2000, Kokko, 2007). The two-part model design allows for finding an optimal strategy given all combinations of individual states through time first and later letting the individual use this strategy in the simulated environment. Competing strategies are evaluated against each other by comparing their effect on the individual's expected reproductive success (Houston and McNamara, 1999, Clark and Mangel, 2000). The integration of physiological aspects in models is suggested to increase their robustnes (Houston and McNamara, 1999, Kearney and Porter, 2009).

3. Summary of Papers (key findings)

3.1 Hormones as adaptive control systems in juvenile fish (**Paper I**)

The first paper focuses on aim 1: the simplification of the endocrinal system, model design and the validation of emergent structures and strategies. In natural fish and organisms of other taxa hormones are often part of very complex networks (Björnsson, 1997, Näslund and Hellström, 2007, Bassett and Williams, 2016). This complexity is seen already in stimuli causing the secretion of a hormone, but also in hormonal cascades or axes necessary to produce, secrete or activate the final hormone affecting a physiological change. Most hormones act in a pleiotropic way (Perez-Sanchez, 2000, Gorissen and Flik, 2014, Orozco et al., 2014), which means that they affect several different phenotypic characters when secreted. In addition to the complexity following a single hormone, there is a network of endocrinal signals in both peripheral and central parts of the organism (Näslund and Hellström, 2007). Especially brain regions like the hypothalamus (Lin et al., 2000, Yoshimura et al., 2003, Volkoff et al., 2005), coordinating and controlling essential body functions, integrate many endocrinal signals at once.

Yet, science is far from understanding how this whole complexity can be mirrored in a mechanistic model. And even if possible, simplified versions would be very useful. Our aim has been at the opposite end: to arrive at an aggregated level of individual hormones that captures the essences of hormonal control of growth in juvenile fish. Through literature studies we identified two hormones and one neuropeptide system important for regulation of growth, metabolism, and foraging activity. The simplification process started in all cases with a comprehensive literature study. For growth hormone and thyroid hormones we reduced the somatotrophic axis and the hypothalamic – pituitary – thyroid axis with corresponding binding proteins, receptors and degrading enzymes, into one factor. These factors are called growth hormone function (GHF) and thyroid hormone function (THF) (Eales, 1988),

respectively. By defining the single functions' main impact on bioenergetics in a juvenile fish, GHF was set to determine the amount of energy allocated to build new structural body tissue. THF was set to regulate standard metabolic rate (SMR) and maximum oxygen uptake, so that the organism must pay for any increase in oxygen uptake by higher energetic costs through SMR. By narrowing the impact of the hormone functions, we could also reduce the number of stimuli causing growth hormone (GH) and associated insulin-like growth factor 1 (IGF-1) secretion to a few ecologically important factors.

Both GH and its mediator IGF-1 are essential for inducing growth related processes in bone, cartilage and muscle tissue (Grossman et al., 1997, Robson et al., 2002, Nilsson et al., 2005). To regulate foraging activity many different signal carriers as hormones, neuropeptides, and neurotransmitters are needed. We first singled out orexin as one of the main molecules. Orexin is associated with higher food intake, but also with other traits, as general arousal, contributing to foraging activity (Dube et al., 1999, Volkoff et al., 1999, Rodgers et al., 2000). It is secreted by the hypothalamus (Lecea et al., 1998), which based on many different central and peripheral signals balances the energy budget of the body (Kalra et al., 1999). Two of those signals are ghrelin and leptin. Ghrelin, as a peripheral hormone, prepares the body for food digestion (Müller et al., 2015, Rønnestad et al., 2017) and is included in the orexin function (OXF). With ghrelin and orexin the OXF initializes the organism for foraging, in a physiological and behavioural way, based on its energetic demands. Leptin secretion is initiated by stored fat (Kurokawa et al., 2005, Cammisotto and Bendayan, 2007), informing the hypothalamus about energy reserve size. In the model we use leptin as a proxy for reserve size, which is one of the two states of the organism. The other state is body size. The organism takes information of both states and they serve as basis for decisions made on optimal hormone levels.

Having constructed the model, the first aim of the PhD work was achieved. In the publication (**Paper I**) this achievement is somewhat toned down, as it appears as a

methods description at the end of the paper. Still, it is a scientific result in itself, and it is the result that the rest of the thesis builds upon.

The results section of **Paper I** adresses the second aim: to use the model to study adaptive control of the phenotype. By running several simulations each with a different food availability, but constant within each simulation, we found emergent strategies in the model output. These strategies were then compared to empirical data for validation. Several physiological relations from the model are in line with empirical data. We found that model organisms growing up in rich food environments have a higher energy turnover and metabolism, thereby enabling their body to grow faster. We also found that the higher growth rates in those organisms are achieved by higher GHF levels, allocating more energy to new structural tissue. Even if THF has no direct effect on growth in the model organism, any increase of GHF is accompanied by an increase in THF levels. In natural organisms, bone and cartilage development is regulated by the combined effect of GH, IGF-1 and thyroid hormones (Robson et al., 2002, Nilsson et al., 2005). Also, the proportion of energy allocated to growth in the model organism is at approximately the rate of energy allocation to growth found in real fish (Cui and Liu, 1990). Using empirical studies as starting point and for validation of model results, theory presented here is derived and directly linked to the work of empiricists. I hope this may facilitate future cooperation between the two fields. From life history theory we know that juvenile fish have to cope with a trade-off between growth and survival (Jachner and Janecki, 1999, Duan et al., 2010).

Growth and survival are intricately related, and we found that hormones play important roles as modulators. While growth is important, not only for maturation (Imsland et al., 1997, Grift et al., 2003), but also concerning the possibility to outgrow predators and increase its chance of survival (Peterson and Wroblewski, 1984, Gislason et al., 2010), survival itself can be lowered by energetic demands coming along with growth (Jachner and Janecki, 1999, Duan et al., 2010). As growing is an energetically costly process (Cui and Liu, 1990) individuals in their

growth phases have to increase their foraging rates to supply growing tissues with nutrients and metabolites. The challenge of balancing increased growth versus survival is the main trade-off for the model organisms. It also links proximate, hormone-regulated physiology to survival as the ultimate cause of adaptations in growth strategies. We found that the optimal solution to the trade-off in a static food environment is a nearly linear growth throughout the juvenile period. We also found that higher growth rates in combination with shorter growth periods result in higher survival at the end of the growth phase. However, instantaneous mortality rates experienced by fast-growing individuals exceed those of slow-growing individuals. This is due to mortality coming along with energetic demands of growth via foraging-related mortality and an activity-related reduction of free scope, which lowers chances of escaping from predators.

The validation of model results with empirical data support decisions made during the simplification process of the endocrinal system (aim 1). It also supports the idea of identifying the most central hormones for adaptive hormonal control of growth strategies in juvenile fish.

3.2 Hormonal regulation of growth and survival in variable environments (**Paper II**)

The second paper continues the investigation of aim 2. It extends from static food availability in the environment to include stochastic food availability. Thereby, optimal hormone strategies under regimes of more or less predictable food availability can be compared.

Food availability varies naturally, often due to changes in abiotic factors such as temperature or light which can be seen in algal blooms or in seasonal growth of temperate forests. In the model, we use an autocorrelated process to simulate variations in food availability. Any changes between consecutive time steps are then limited within a certain range. Thereby, environments with both high and low

variability in food availability can be simulated. For the comparison made in this article, we chose a rather high autocorrelation coefficient, which allows food availability to vary, but at the same time, makes the environment somewhat predictable, as changes only occur in a certain range.

By comparing optimal strategies from static environments to that of variable food environments we found clear differences in hormone levels, energy allocation and growth. The higher food availability is, the faster fish grow and even more so in temporarily changing envirments where fish takes the opportunity to harvest resources when aundant. This growth is accomplished by high levels of all three hormones: OXF increases intake, GHF allocates energy to growth processes building new soma and THF upregulates SMR and allowes for higher oxygen uptake. This enables the individual to have higher activity rates without increasing its mortality risk due to reduced free scope.

We found that for fish growing in environments with predictable but stochastic food availability, model results are similar to results from the constant environments. Yet, we found that hormone levels in rich food environments are on average slightly higher in stochastic environments. Fish living in constant environments do not have the possibility to wait for better times, nor a reason to fear the worse. They have to forage and grow under the given environmental factors and, associated therewith, experience a high instantenous mortality.

We found that use of reserves is a second important difference between fish growingunder constant or stochastic environmental conditions. While fish experiencing constant food availability do not have a need for reserves, fish from stochastic environments use them to move risk in time. We found that when food availability is low they use energy from reserves instead of foraging and limit associated instantenous mortality. When food availability is high, they use energy from reserves to support their high growth rates. In both cases, they deplete their energy reserves. Building up reserves is done at intermediate food availabilities by

keeping OXF at a medium level. This reduces energetic expenses caused by growth and metabolism through hormonal regulation.

We found an important difference when food gets scarce. Individuals living in stochastic environments then use their reserves to counteract the effects of food scarcity. During this period all activity, SMR, growth and foraging, is reduced to a minimum. In this way instantanous mortality is reduced. The difference in optimal policy for fish that permanently live in poor conditions (**Paper I**) and fish that for a while experience poor conditions, shows the importance of future expectations for the optimal policy. In **Paper II**, individuals can utilize reserves in the hope and expectations that the poor situation will come to an end. But they will also, as mentioned above, have slightly higher activity during other conditions than individuals in stable versions of those conditions, so that they build reserves to meet future challenges. If reserves are almost depleted, the fish change their strategy and increase levels of OXF and THF to to activate food-searching behaviour to avoid death by starvation.

The model results also reveal differences in experienced mortality due to variation in growth strategies. Fluctuations in food availability force individuals to make use of accessible energy when food availability is high. Therefore, both foraging-related mortality and scope-related mortality are higher in stochastic environments when food access is high, than in comparable constant environments. The opposite is true when food is scarce. The wait-and-see approach of fish experiencing low food availability in stochastic environments reduces their foraging- and scope-related mortality via reduced acitivity of the individual. Thereby, the individual expiriences a lower instantanous mortality rate than fish in constant environments.

By studying an intermediary level of phenotypic control, here the hormone strategies used to achieve growth, we can see that certain combinations of hormone levels can be advantageous under differing environmental conditions (Aim 2). This makes endocrinal strategies a factor on which evolution, by natural selection, can act. Hence,

hormones can be seen as functional units giving the organism a foresight and regulating changes concerning growth, survival and reproduction.

3.3 Hormonal regulation of the phenotype into environmentally appropriate Pace of Life Syndromes (**Paper III**)

The aim of the third paper was to study changes in optimal hormone strategies and life histories along an ecological gradient. Here we used the model developed in the first two papers of this thesis (Weidner et al., 2020, Jensen et al., subm.) with an extension concerning predation risk. The gradient was defined as variation in the type of predation regime, while total predation pressure was kept constant. At one end of the gradient, strategy-independent mortality, affected by the size of the fish, e.g. mortality due to gape-limited predators, dominates the total mortality risk. Moving towards the opposite end, mortality affected by body size becomes less important and strategy-dependent mortality, which is related to the individual's activity, gains in importance.

Simulations along this gradient reveal that predation regimes are an important factor driving natural selection towards more risk-prone and fast-growing life histories when strategy-independent mortality contributes most to total moratlity. The opposite is true for strategy-dependent mortality. Then selection drives adaptation towards risk-averse and slow-growing individuals. Hormone functions in the model organism play a crucial role in regulating and synchronizing physiological and behavioural traits of the phenotypes. To achieve high growth rates, the individual needs to increase foraging activity and metabolism, resulting in higher oxygen use. Accessible energy can then be directed to growth and higher support higher growth rates.

Reserves play an important role for adaptations to predation regimes. For all predation regimes, reserves are used when food gets scarce and reserves are built when food availability is intermediate. In times of high food abundance, energy stores get depleted to support growth. By using energy from food and from reserves, higher

growth rates can be accomplished. Thus, the change in priorisation supports faster growth and enables the individual to leave vulnerable small body sizes. Comparing individuals from populations adapted to different predation regimes, we found a difference in when individuals, by hormonal regulation, change energy allocation rules. For populations adapted to high strategy-dependent mortality, a relatively small reduction in food abundance initiates a change of priorities from growth to energy storage. Also, the amount of energy stored in reserves is higher in those populations. Individuals from populations adapted to high proportions of strategy-independent mortality are characterised by relatively small reserves and late initiation of energy allocation to reserves. The high rate of energy turn-over and growth, when food is abundant, depends on high oxygen use in physiological processes. This use of oxygen leaves indivudals in a vulnerable situation, as fleeing from predators requires oxygen either directly (aerob activity) or indirectly (recovery after anaerob activity). THF counteracts this oxygen need by increasing oxygen uptake rates. This is an energetically costly process.

By evaluating adaptations from a physiological, behavioural and life history view, instead of evaluating isolated traits, we find pace of life syndromes at the endpoints of the gradient. We can compare these syndromes to existing fish types, and thereby use empirical studies to validate some of our results. With an increasing proportion of strategy-dependent mortality model fish show similarities to demersal bottom-living fish, e.g. plaice. At the opposite end we find similarities to pelagic fish, e.g. mackerel.

4. General Discussion

When philosophers make short lists of the most influential thinkers in Western culture, Aristotele is usually included. He acknowledged four types of causes: the material, formal, efficient and final cause (Hankinson, 1998). An example of the final cause (called *telos*) is that it rains because the soil needs it. Modern meteorology, physics and chemistry are not based upon the existence of a *telos*. Explanation in these sciences fall under the material and efficient causes. This is why the reductionist paradigm is so successful. Also, many biological disciplines work in this manner, although evolution by natural selection has established purpose in nature: the geometry of the haemoglobin molecule must obey the laws of physics and chemistry, but that is not sufficient to explain its structure. One must also consider how the genes coding for the molecule are conserved and copied by natural selection due to the effect of the molecule on the survival and fecundity of the organism (e.g. (Windsor and Rodway, 2007)).

While there are just a few genes involved in the production of haemoglobin (Hardison, 2012), there is a high number of known and unknown genes involved in animal behaviour. Thus, as the building of the phenotype from genes via development, the nervous system, emotions, and hormones is only partly understood, researchers will still have to utilize some or much of Grafen's phenotypic gambit in studies of behaviour. And it explains why physiologists have attempted to search downwards to the genes for explanation while evolutionary ecologists have searched upwards to natural selection.

In the POLS literature, one finds examples that place causation in the Aristotelian efficient-cause (e.g. Chung et al., 2018, Ricklefs and Wikelski, 2002, Glazier, 2015) as well as in the final cause (e.g. Salzmann et al., 2018). The truth, in biology, is always a combination. In this thesis, I have tried taking the final cause one step down in the levels of explanation, and modelled how hormones also can be part of the top-down causation. I cannot claim that we have revealed great secrets, but we have made

a starting point for new models that can combine forcing from the top with forcing from the bottom.

While we have not studied how genes code for hormones or how hormones are synthesized from building blocks, we have shown that the hormones can work together to establish an evolutionarily optimal phenotype.Variation in phenotypes associated with the pace of life syndrome can be achieved by up- or down-regulation of one or more members of the suite of hormones that together orchestrate the phenotype.

The 3-component hormonal system in our model is at the very minimum for detecting complex interactions. Further, the one-week time resolution in the model will only reveal average strategies and tactics over this period, and the hormones are also free to change from week to week. Thus, dynamics caused by both fast and very slow production and destruction of hormones will not appear in our model. Yet, we see indications that evolutionary optimization at the level of hormones leads to conflicts within the phenotype not visible at the usual level of optimization models: that of behaviour. It is likely that these conflicts would have grown rather than disappeared with both shorter time steps and some more hormones. Maybe will these conflicts maximize at an intermediate number of pleiotrophic hormones, so that the very high diversity of hormones in most species is an evolutionary attempt to specialize each hormone to fewer tasks, thus simplifying the challenge of optimal regulation of each.

The time frame in which hormones act and their pleiotropic nature allow for regulating the individual to changing environments on short time scales, e.g. weekly, but also for adaptation on long time scales, e.g. evolutionary. There is no other system in current organisms that could take over the tasks solved by the endocrinal system. Even if the nervous system is able to signal, control and process information, it is working at a much higher energetic cost. The speed of electrical signalling, compared to endocrinal signals, is much faster and could therefore be a disadvantage for information that shall persist over some time. Many processes need to be

coordinated to achieve a certain state, e.g. for reproduction. This could be impeded by continuously incoming information about changing external or internal factors thereby changing the prioritized state of the individual. Thus, the endocrinal system is an adaptive information translation system, which coordinates and combines effects on differents traits as energy-use and survival, thereby having a role in inceasing fitness.

Considering the effects of predation regimes on life histories and POLS (**Paper III**), changes in community structures due to invasive species should not be underestimated. Main causes of invasion today are translocation of organisms and alterations of landscapes by humans (Mann, 2011). A reduction in number of invasive species can not be expected in near future. Any invasion can result in changed predator regimes and consequently changed predation pressure due to certain behaviours. Conclusions from **Paper III** could be important for assessments of invading species.

The three papers contributing to this thesis are theoretical and based on the model developed and described in **Paper I**. Even if the model is based on empirical studies as far as possible, and its results are validated and compared to empirical studies, models should be subject of a "modeling cycle" (Grimm, 2005). This includes development of the model, testing and analysing of its results and communicating them. In an iterative process a new round of formulating hypotheses, developing and testing the model can be done, in which results of the previous round are considered. In this process, called strong inference (Platt, 1964, Fudge, 2014), empirical knowledge should be valued when developing and validating the model and its results. The model presented here has undergone a development from the original model (**Paper I**), to include a stochastic food environment (**Paper II**) and test for evolutionary consequences of changes in predation regimes mediated via the endocrine system (**Paper III**). By communicating and publishing our results, we aim for broader discussion on projects combining different levels of analysis.

A further development of the ideas worked on in this thesis should include both theoretical and empirical studies. In the following I will discuss possible extensions of the current model and the integration of ideas presented here, in an individual-based model (IBM). I will also suggest some empirical approaches.

In this thesis I use a dynamic optimization model in which fish growth is regulated by three hormone functions. Both thyroid and growth hormones with their associated hormone system, receptors, binding proteins and so on, are pleiotropic. In addition to effects on growth (Robson et al., 2002, Nilsson et al., 2005), metabolism (Heilbronn et al., 2006, Kitano et al., 2010, Velez et al., 2019) and development (Youson et al., 1994, Delgado et al., 2006), many studies have documented their effect on reproduction in many different taxa as fish (Legac et al., 1993, Swapna and Senthilkumaran, 2007), birds (Ikegami and Yoshimura, 2013, Mohammadi and Ansari-Pirsaraie, 2016), mammals (Legac et al., 1993, Watanabe et al., 2004, Rani and Kumar, 2014) and reptiles (Sparkman et al., 2010). The fact that both hormone systems have a major impact on reproduction is not taken into account in the current version of the model, as we only focus on the juvenile phase. In the life history triangle three traits are of importance for life history patterns; age at maturation (growth), survival and reproduction (Kawasaki, 1980, Winemiller, 1992). By extending the model to **include maturation**, we could not only extend hormonal effects on life history and POLS, but study the regulation of growth by hormones when considering the whole triangle. This extension would allow us to see changes in hormone strategies and trade-offs at the shift from juvenile to adult fish. A possible research question could focus on the differences of energy allocation between storage and growth in changing food environment between juvenile and adult fish. The extension would also allow for implementation of sex hormones, e.g. testosterone and estrogens. Consequently, fish would be defined as male and female and differences in allocation strategies could arise.

For all simulations in this thesis a **time resolution** of one week is choosen. This limits hormonal strategies to average strategies. By increasing the resolution,

hormonal strategies could regulate physiological processes and behaviour at a time scale closer to their natural time scale. Trade-offs concerning growth and energy-allocation could differ from the trade-offs we see now. Maybe shorter time periods (less than one week) with low food availability would allow prioritizing growth instead of switching to energy storage, when growing up in habitats with high strategy-dependent mortality? In habitats with high strategy-independent mortality a similar period with little food could be without consequence for shifts in energy allocation. Also, an increase of the time resolution could allow for implementation of new hormone functions. Hormones acting on short time scales, e.g. adrenalin, cannot be implemented when calculations are on a weekly base. New hormone functions would also influence trade-offs described in this thesis and make the model organism more complex. By increasing the complexity of the endocrinal system in the model organism, the system would resemble natural endocrinal sytems even more.

Several studies have suggested a **genetic basis of POLSs** (Santostefano et al., 2017, Dammhahn et al., 2018, Immonen et al., 2018). Even if single genes or gene sequences can be related to POLS, a gene never acts on its own, but as part of a greater system, the genome. Also genes come in different variants, alleles, which can depend on the frequency of other, competing, alleles (Sokolowski et al., 1997, Fitzpatrick et al., 2007). To study the **evolution of POLS under frequency dependency**, a dynamic optimization model is inadequate, as individuals pass through their juvenile phase independent of each other. In contrast to optimization models, individual-based models (IBMs) make it possible to simulate a population of organisms that interacts and influene their conspecifics, creating a frequency-dependent environment. An already existing IBM, the AHA-model (Giske et al., 2013, Budaev et al., 2018, Budaev et al., 2019), could be used to implement mechanisms and even functions from our optimisation model. In AHA, model organisms collect information about their surroundings, as light, food availability, and competitors. They also collect information from internal states such as their stomach fullness and their total body mass. Based on the external and interal

perceptions each fish updates an internal model of itself and its environment, on which decisions are based. Every new impression challenges the current internal model and feeds into competing brain states related to emotions or homeostatic drives, such as hunger, fear, thirst, pain, need for rest, exploration tendency, sexual arousal, etc. This completion among brain states may result in a global organismic state (GOS), which, on the level of the whole individual, influences attention, physiology, and decision-making. For example, the model organism experiences an environment with high predator density and the internal model reflects this. The dominant GOS then becomes fear and leads to fear-related behaviour like decreased foraging, longer periods of hiding and so on.

Thus, the dynamics of behaviour in the AHA-model are driven by very fast dynamics of sensing and emotions. The inclusion of hormone dynamics could affect individual behaviour in two ways. First, some hormones, and especially steroid hormones like growth hormone, have relatively long half-life periods. This results in hormone effects long after secretion. For GOS-dependent model organisms, this would lead to an inertia in maintaining and changing global organismic states. Second, building the internal model based on external and internal impressions could be influenced by hormones. Beside physiological mechanisms, hormones also influence our sensory perceptions. While senses have a bottom-up effect on the animal's internal model, competing brain states, emotions, and behaviours, the hormone system can be seen as a dynamic part of the organism's adaptive top-down regulation of its physiology and behaviour. Hormonal modulation may up- or downscale the sensitivity to external as well as internal signals. Thus, hormones would influence the perceptions the internal model is build on and then also the resulting GOS. Studying the impact of internal models and limited sensory perception due to hormonal regulation would increase the realism in models of decision-making. It would also have implication for empirical studies, as decisions made under laboratory conditions could be influenced by earlier impressions.

The main aim of this thesis is to combine proximate and ultimate explanations for juvenile fish growth, thereby including physiology and evolutionary biology. To do so, we based as much work as possible on empirical studies and now it seems natural to suggest a way back to empirical studies in order to test new hypotheses and validate our theoretical results. As discussed earlier (chapter 1.1), cross-disciplinary work should let us make assumptions and give us insights we could not have had when working in an environment where the question of "how" a trait is realized is considered in isolation from asking "why" a trait is realised. I therefore suggest the following hypotheses for future empirical work.

Qualitative differences in predator profiles result in intraspecific differences in growth strategies and POLS in prey species. This hypothesis is the result of **Paper III**. Natural mortality is difficult to measure and assessments exist only for few species (Vetter and Vetter, 1988, Julliard et al., 2001, Gislason et al., 2010). For example in exploited stocks of cod a relationship between size-related mortality and growth has been shown (Swain et al., 2007). While the direct effect of predation is the killing of prey, the indirect effect can come by olfactory or visual cues (ecology of fear) (Brown et al., 1999, Leahy et al., 2011). The fear of encountering a predator can result in behavioural changes (Brown, 2003). In gobies, the presence of predator cues can result in reduced foraging and growth rates (Steele, 1998, Steele and Forrester, 2002). In model results we can see these behavioural changes in form of faster or slower POLS, and our model furthermore suggests how changing hormone profiles can be part of the picture. There are studies comparing populations experiencing different predation pressures, but the difference usually lies in the total mortality risk, not the type of risk experienced (Stephenson et al., 2015, Auer et al., 2018) (but see (Palacios et al., 2018)). Also the observed differences have not been extended to hormones. Thus, studying local adaptations to differing predation regimes in one species could validate model results and would provide a better understanding of predation regimes as drivers of differentiation in POLS.

Empirical studies showing behavioural, physiological and morphological changes in traits along an established slow-fast continuum seem to be rare, but could strengthen the POLS literature. This thesis shows that POLS-related traits change in a coordinated manner and changes in all traits together underlie adaptations to different environments. Ecological drivers for the evolution of POLS have also been shown for Eastern mosquitofish (*Gambusia holbrooki*) (Polverino et al., 2018). The importance of ecological factors for detection of POLS and correlated traits has been discussed under the aspect of plastic responses (Montiglio et al., 2018). If these phenotypic differences are maintained with the aid of genetic variation, then a purely phenotypic method such as dynamic optimization would not be the best tool to study them. A tool that traces the build-up and maintenance of genetic variation would be better, such as an individual-based model of a population, where genes evolve in a genetic algorithm. As already mentioned, the AHA model does this (Budaev & al 2018), but it is limited to a very simple hormonal control function: up- or down-regulation of sensitivity to types of sensory information through development, via unnamed mechanisms (Giske & al 2013). Thus, implementing the hormone functions of **Paper 1** would enable frequency-dependent evolution of hormonal variation underlying POLS-related personality types. This tool could then be specific enough to mimic natural populations, and thus be challenged much more realistically by empirical studies than our current model, as asked for by (Dammhahn et al., 2018). Studies on slow-fast continuums or POLS are often limited to one species and few traits (Stephenson et al., 2015, Auer et al., 2018, Damsgård et al., 2019). I hope this thesis can be an encouragement to perform multi-disciplinary studies examing species and populations along ecological gradients.

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Paper I

Jacqueline Weidner, Camilla Håkonsrud Jensen, Jarl Giske, Sigrunn Eliassen & Christian Jørgensen

Hormones as adaptive control systems in fish

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RESEARCH ARTICLE

Hormones as adaptive control systems in juvenile fish

Jacqueline Weidner*, Camilla Håkonsrud Jensen, Jarl Giske, Sigrunn Eliassen and Christian Jørgensen

ABSTRACT

Growth is an important theme in biology. Physiologists often relate growth rates to hormonal control of essential processes. Ecologists often study growth as a function of gradients or combinations of environmental factors. Fewer studies have investigated the combined effects of environmental and hormonal control on growth. Here, we present an evolutionary optimization model of fish growth that combines internal regulation of growth by hormone levels with the external influence of food availability and predation risk. The model finds a dynamic hormone profile that optimizes fish growth and survival up to 30 cm, and we use the probability of reaching this milestone as a proxy for fitness. The complex web of interrelated hormones and other signalling molecules is simplified to three functions represented by growth hormone, thyroid hormone and orexin. By studying a range from poor to rich environments, we find that the level of food availability in the environment results in different evolutionarily optimal strategies of hormone levels. With more food available, higher levels of hormones are optimal, resulting in higher food intake, standard metabolism and growth. By using this fitness-based approach we also find a consequence of evolutionary optimization of survival on optimal hormone use. Where foraging is risky, the thyroid hormone can be used strategically to increase metabolic potential and the chance of escaping from predators. By comparing model results to empirical observations, many mechanisms can be recognized, for instance a change in pace-of-life due to resource availability, and reduced emphasis on reserves in more stable environments.

This article has an associated First Person interview with the first author of the paper.

KEY WORDS: Hormone, Dynamic state-dependent model, Strategy, Growth, Survival, Allocation

INTRODUCTION

It is a central aim of biology to understand how evolution has led to a specific organism design through natural selection. As Tinbergen (1963) pointed out, any trait can be understood both in terms of its mechanism and its evolution, and the philosopher Daniel Dennett (2017) has simplified this into two questions. If, for example, one is interested in fish growth, one may first ask '*How come* fish grow?' The discipline of physiology has excelled at answering this type of question about underlying mechanisms, and has detailed triggers, pathways, intermediates, regulation, development and function from the molecular level to that of the organism. There is another set of explanations for fish growth if one asks: '*What* do fish grow *for*?' 'What for' questions are about the adaptive significance, about the effects a trait has on survival, growth, reproduction and ultimately fitness. This evolutionary dimension introduces *purposiveness* to biology (Dennett, 2017): a goal-directedness that goes beyond blind chains of causation and transcends Hume's billiard balls that crash into each other. Rather, processes occur to fill a purpose, to obtain some kind of aim, for example feedback processes that restore homeostasis, or drives or urges that ensure survival, growth and reproduction. It must be emphasized that this is not an externally imposed or top-down purpose. It is a historic consequence of natural selection, where alleles with positive effects on survival and reproduction become more common in the gene pool, and their consequence is that organisms appear as goal-driven in their development, physiology, endocrinology, cognition and behaviour (Andersen et al., 2016; Budaev et al., 2019; Giske et al., 2013).

'What for' questions have been addressed by evolutionary ecology, life history theory and behavioural ecology, where empirical experiments and observations have often been inspired by theoretical considerations that have had one important limitation: they have typically ignored the proximate level of 'how come' questions. This was epitomized by Alan Grafen as the phenotypic gambit, inspired by the chess move where one makes a sacrifice to gain a longer-term advantage (Grafen, 1984). The phenotypic gambit was a methodological tactic where one tossed away all the mechanistic detail and simply assumed unbounded phenotypic flexibility. Then and now, this was in many cases a necessary assumption to be able to answer 'what for' questions. If models concluded that a trait had an adaptive advantage, the evolutionary ecologist would expect to see that trait to have evolved in real organisms in the wild. Any physiologist will immediately react to this as naïve and utterly unrealistic: real traits originate from genes, are built through biochemistry, obey the laws of physics, and any information used must emerge from a sensory organ or use local molecules directly. The organisms that live today share many design features that have evolved precisely because they allow flexibility within the boundaries set by these constraints (Giske et al., 2014). Over time this has led to descendant lineages that were more likely to evolve to fill new niches and respond to new selection pressures. The combination of 'how' and 'what for' questions, thus, reveals insights that one of them alone could not give (Sinervo and Svensson, 1998). On the other hand, the traditional separation of mechanisms from the individual's experienced selection pressures or ecological challenges tears them out of a natural framework of constraints. It also builds on the assumption that selection pressures influence underlying mechanisms much less than the actual behaviour or adaptation they produce (Garland et al., 2016).

In this paper, we focus on one architectural design feature for control of the organism – its hormone system – and with a model we

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ask several questions that we believe are useful to stimulate thought both among physiologists and evolutionary ecologists. For example, are key hormone systems sufficient to enact the adaptive flexibility seen in growth across different environments? Are there ways in which we can conclude that the major hormone systems are adaptive? If we treat the model as a thought experiment with unlimited flexibility in hormone expression, will observed correlations emerge between environments and hormones? Between hormones? And with ontogeny? The model is about growth and related survival in juvenile fish, but more importantly it aims to show how one can partly overcome the phenotypic gambit, not only in the model specification, but hopefully also by helping scientists from the two disciplines in asking and answering questions together.

It can be instructive to compare our process-based model with other modelling approaches to better see the type of questions we can reach for. One type of well-known modelling tool in physiology is the dynamic energy budget models [DEB, (Kooijman, 2010)]. These follow resources and energy in great physiological detail from ingestion to growth and reproduction, and may provide a good fit between predicted growth patterns and those observed in experiments and in the wild. Somewhat caricatured, one can describe DEB as 'feed-forward bioenergetics', where processes run as fast as resources or constraints allow. This perspective is similar to a combustion engine where the amount of gas fed into the carburettor determines the engine's power and speed. Models of feed-forward bioenergetics are designed to question what happens to metabolic processes if more or less food is processed, when external conditions change, for example temperature, or when there are extra costs due to e.g. disease or reproduction. These are analogous to how fast a car would go if it was loaded heavily with passengers, if cooling was difficult on a particularly warm day, or if one of the spark plugs didn't fire. In practice, DEB models can also lie in between and study how physiology changes to maintain a set growth rate (e.g. Lika et al., 2014), but DEB rarely questions the ultimate drivers that determine the adaptive growth rate under specific circumstances.

In contrast, our model optimizes survival through the juvenile phase, where the optimal growth rate emerges from the effects of growth on fitness. These may depend on the abundance of predators, food availability or duration of the growth season. Here, behaviour and physiology have to provide the resources required to achieve the target growth rate. This can be described as 'by-demand bioenergetics'; a goal-driven control system that translates fitness incentives emerging in ecology into physiological responses that endow the phenotype with a performance to fulfil the set goal. This would be analogous to how hard the driver presses the gas pedal, which can depend on the speed limit or whether the driver is heading for the nearest hospital with a critically injured patient. The car is a tool to achieve a goal in the driver's mind, much like the physiology of an organism has potentials that can, if regulated appropriately, achieve fitness. It should be noted that DEB modelling acknowledges how organisms can have flexible phenotypes whereby energy use varies with environmental characteristics (see Lika et al., 2014 for an overview). While this is referred to as a 'supply-demand' spectrum (Lika et al., 2014), the focus is on how sensory organs and behaviour permit a flexible phenotype, not on how the resulting bioenergetics is purposeful or goal-driven because of its effects on fitness in the sense of Tinbergen (1963) or Dennett (2017).

There are several ways in which control mechanisms can regulate and interfere with the individual's bioenergetics. In a system that is goal-driven, a certain amount of energy will be directed to mechanisms needed to achieve the goal. The process of allocation of limited resources towards competing uses (Fisher, 1930) is therefore essential. Also, as resources must be acquired before they can be distributed, the acquisition rate is of importance. Often models deal with either acquisition or allocation. Here we combine the two-in-one model and under-one-control system. In this way, 'by-demand bioenergetics' can drive the phenotype towards its goal by increasing the goal-directed energy supply through acquisition and by reshuffling allocation among potential uses. Upregulating 'by-demand bioenergetics' in such a way can push the organisms into a state of fast growth and early maturation, or the opposite, as would best achieve fitness in a given environment. From an evolutionary point of view this would mean that life history changes from slow to fast or vice versa.

We have used the method of dynamic programming to connect short-term decision to fitness, as is common practice in evolutionary ecology (Clark and Mangel, 2000; Houston and McNamara, 1999). In the same tradition, we have also focused on a part of the full life cycle (juvenile growth up to 30 cm) by recognizing that survival during this phase is a prerequisite for achieving fitness later in life. To be specific about the goal-directness of growth in a proximate and mechanistic perspective, we treat the phenotype as having potential for a range of physiological rates, and focus on a simplified set of hormones as the control system. Because there are hundreds of hormones and associated signalling molecules in a typical fish or mammal, it was necessary to simplify to a level of complexity that is easier to grasp and analyse. We therefore first describe how we have interpreted the major regulatory routes that control growth in fish, and end up using three hormones and a neuropeptide that each play a specific role in our model. To a physiologist this simplification is most certainly incomplete as it definitely leaves out important elements, but our aim is to stimulate thinking, and we therefore ask the reader to follow us into this intermediate level of complexity. We now first describe how we have implemented our model, before we use the model to point to some interesting insights of the hormone system as adaptive, and ways forward to further bridging the proximate 'how come' and the ultimate 'what for' traditions in biology.

Model

The model organism is a generalized juvenile fish, and we choose parameters mostly from Atlantic cod (*Gadus morhua*), which is a well-studied species. The model follows juvenile fish as they grow through a size window where they typically remain immature. During this juvenile phase we let internal mechanisms like metabolism and growth be regulated by growth hormones (GHs), thyroid hormones (THs) and the neuropeptide orexin. They determine growth, metabolic rate and appetite, respectively, but importantly for the model they are also jointly involved in trade-offs related to risk (Fig. 1). The model also includes a role for the hormone leptin in signalling size of reserves.

We use a state-dependent dynamic model (Clark and Mangel, 2000). This algorithm first optimizes a strategy that can be considered the evolutionary adaptation to a certain environment. In the case of this model, the strategy is the optimal hormone levels for any combination of fish size and energy reserves. When the optimal strategy has been found, we investigate this adaptation by simulating individuals that live in the given environment and use the calculated optimal policy, and we record its trajectory of growth, hormone expression and individual states.

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RESULTS

The optimal strategy for the hormone profile changed during the fish's growth phase, resulting in a near-linear length growth and decreased mortality rate over time (Fig. 2). While energy gain and oxygen budgets were relatively stable per unit of body mass, mortality decreased with size. The optimal level of growth hormone function (GHF) fell throughout the growth phase (Fig. 2A), but as the effect was relative to body size, the resulting growth in length was near linear (Fig. 2D).

The optimal level of orexin function (OXF; green) was relatively constant throughout the growth phase (Fig. 2B), which resulted in a stable food intake rate per unit of body mass. Energy from feeding was allocated to standard metabolic rate (SMR), specific dynamic action (SDA), soma, metabolic processes involved in conversion of food to reserves and growth, and the activity associated with searching for food (Fig. 2E). Since the food environment was not changing over time, the fish did not benefit from storing energy in reserves, but rather allocated all somatic investments towards structural growth (Fig. 2E).

There was some variation seen in the levels of thyroid hormone function (THF) over the growth period for the fish (Fig. 2C). This variation was too small to have a visible effect on SMR or maximum oxygen uptake per unit of metabolic mass (Fig. 2E,F). However, both SMR and maximum oxygen uptake for the individual increased due to increases in total body mass (data not shown).

The instantaneous mortality rate decreased during development (Fig. 2G), mainly because size-dependent mortality (grey area, Fig. 2G) is smaller for larger fish (Eqn 22). Foraging mortality (Eqn 23), scope-related (Eqn 24) and active-while-vulnerable mortality components (Eqn 25) also dropped. Foraging activity and free scope were relatively constant, hence changes in these mortality components were mainly due to lower predation risk with increasing size.

If we study how the optimal hormone strategies change along an environmental gradient in food availability, we see that the levels of OXF, GHF and in particular THF were higher in environments with more abundant food (Fig. 3A). Individuals in rich food environments grew faster, and had higher oxygen uptake and better survival probabilities. Faster juvenile growth requires increased energy intake, which resulted in higher SDA and conversion-related costs. Oxygen requirements also increased, which selected for higher THF levels that increased maximum oxygen uptake and secured free scope (Fig. 3C). THF also upregulated SMR, hence the optimal hormone level depended on the availability of energy in the environments and costs in terms of energy and mortality that came with gathering food. The energy allocation trade-off, between investments in maintenance and survival on the one hand and growth on the other, changed with food availability. Throughout the growth phase this trade-off was influenced by THF, which deducted energy to support a higher metabolic rate that in turn increased escape probability from predators. As energy was more accessible when food abundance was higher, activity costs were unchanged even when intake increased (Fig. 3B). Due to higher hormone levels, fish in habitats with high food availability had higher growth rates, intake and SMR (Fig. 3).

When comparing oxygen budgets (Fig. 3B), there was a slight increase in free scope from the poorest to the richest food environments. THF enabled the organism to increase its free scope despite higher oxygen use, thus permitting higher growth and foraging through the other hormones. Oxygen used for preparing metabolites for new soma reduced free scope, while THF worked against this process by elevating maximum oxygen uptake.

Simplified, GHF sets energetic needs, OXF meets the needs by determining foraging activity and providing metabolites for growth. The increased energy turnover has to be supported by THF, regulating maximum oxygen uptake to reduce mortality rate when energy is readily accessible and high turnover desirable (Fig. 3D).

Adaptations in hormone levels caused fish in rich environments to have a shorter juvenile phase (Fig. 3E). Despite similar instantaneous

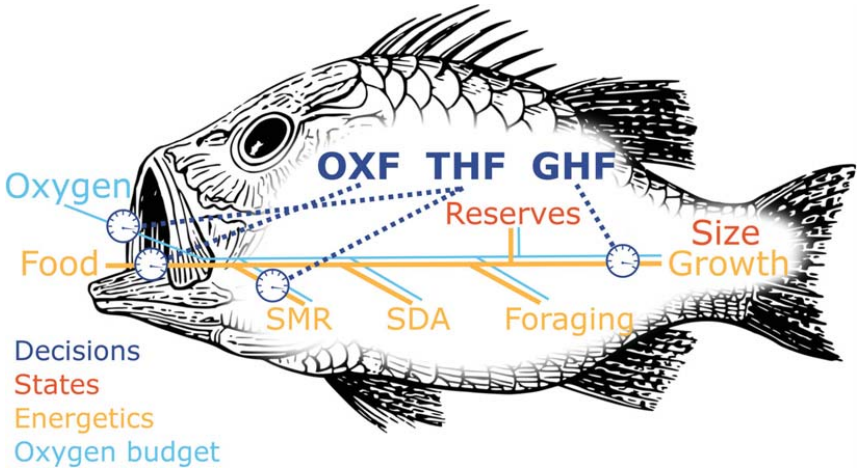

Fig. 1. Energetics and endocrinology of the model organism. Energy from food is made accessible for the body by digestion (SDA). This energy is then used in metabolism to maintain life-supporting metabolic pathways (SMR) and supply the organism with oxygen. Also, activities like foraging require energy. The surplus is stored in reserves. Hormonal regulation determines the foraging intensity (OXF), increases or decreases of metabolism rates (oxygen uptake and SMR) and the allocation of resources to growth (GHF). Throughout the simulations, decisions regarding hormone levels are based on the two individual states of the fish – reserve size and body size.

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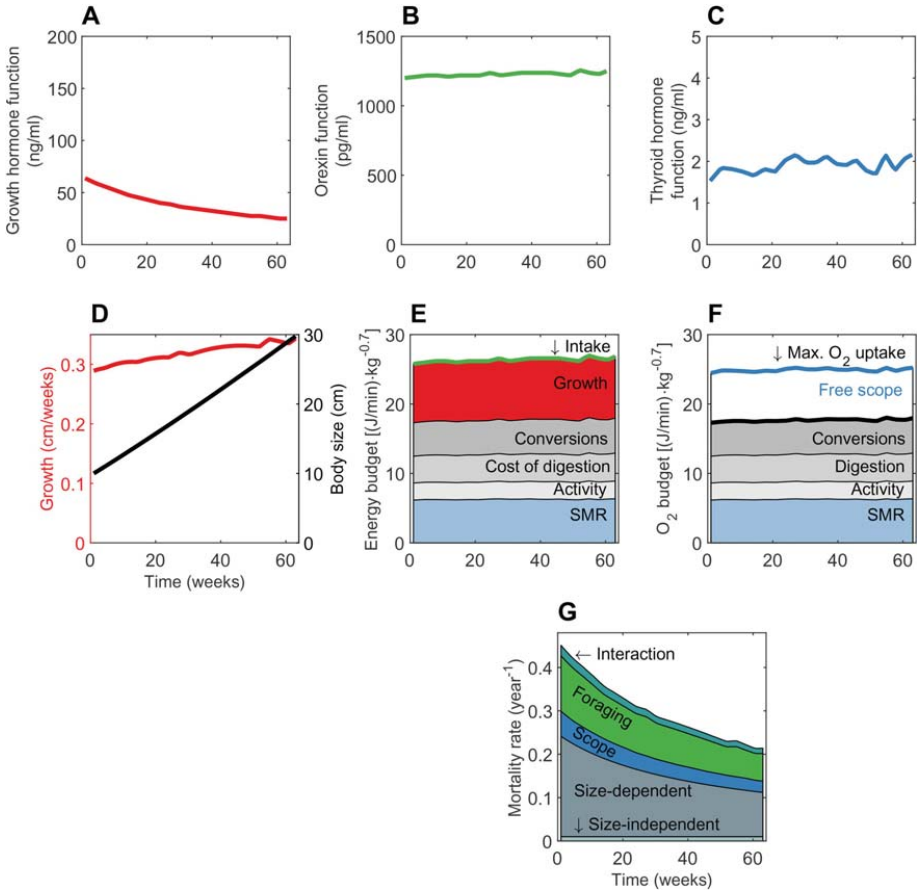

Fig. 2. Endocrine regulation, energy and oxygen budget, mortality and growth of juvenile fish in a stable food environment. The simulation starts when the fish is 10 cm and ends at 30 cm, with the x-axis giving time (in weeks since 10 cm) in all panels. (A) Growth hormone function, (B) orexin function and (C) thyroid hormone function are given as a function of time. (D) Weekly growth and accumulated body mass, (E) energy budget, (F) oxygen budget and (G) mortality rate.

mortality rates (Fig. 3D), the probability of surviving to the end of the growth phase differed substantially between food environments because the duration of the growth phase was longer when food was scarcer.

DISCUSSION

Most evolutionary optimization models of animal growth and survival focus on behaviour, size or other phenotypic traits while the internal regulatory processes are often ignored (Fawcett et al., 2014; Grafen, 1984). For fish, this includes social behaviour (Rountree and Sedberry, 2009; van der Post and Semmann, 2011), diel vertical migration (Burrows, 1994) and habitat choice (Fiksen et al., 1995; Kirby et al., 2000), but see Salzman et al. (2018). Here we take the opposite perspective, and study optimal internal regulation by hormone systems for animals that cannot choose their external environment. Obviously, most animals can do both at the same time, and habitat selection can have a direct impact on the physiological needs and priorities of the animal (Elton, 1927). But by removing the movement options in this model, we can isolate how internal mechanisms can be used to optimize trajectories of growth and mortality risk. We found variation in optimal hormone levels across different food environments and throughout ontogeny. The results in this paper are the outcome of an evolutionary optimization model based on an assumed connection between survival through a juvenile size window and lifetime fitness. We modelled adaptive evolution in three hormone functions, GHF sets the fitness-optimizing growth rate, OXF provides the required resources through appetite control and foraging, while the THF adjusts trade-offs between bioenergetics and survival. Effects of the hormonal control were evident in growth patterns, energy allocation, oxygen budget, activity levels and in survival.

Increased food availability enables organisms to grow faster, which is achieved by speeding up metabolism to accommodate increased physical and biochemical activity. Model fish adapted to high food availability by having higher optimal concentrations of GHF and THF than those adapted to food-restricted habitats

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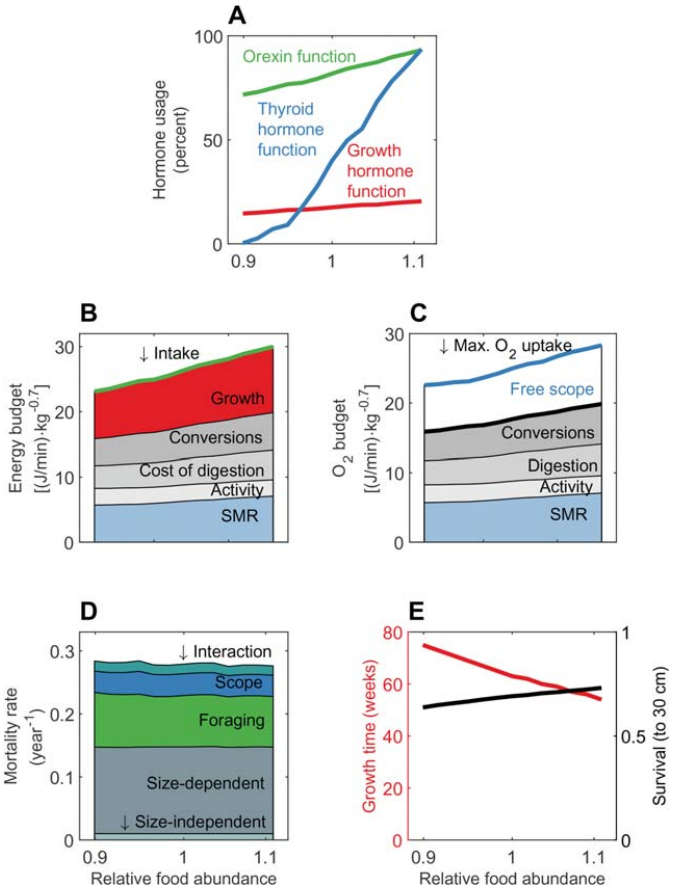

Fig. 3. Environmental influence on hormone levels, energy and oxygen budgets, survival and growth duration. The x-axis is the same in all panels, with a gradual increase in food abundance relative to the average food environment as used in Fig. 2. Simulations of fish in 13 food environments were compared at individual length around 20 cm. (A) Hormone levels. (B) Energetic costs from growth and metabolism. (C) Free scope as the difference between maximum oxygen uptake and the sum of processes consuming oxygen. (D) Five different components contribute to mortality. (E) Growth time and survival over the entire juvenile life phase of the fish.

(Fig. 3). Empirical studies testing for changes in hormone concentrations in relation to diet quantity focus on short-time experiments, often with feeding–starvation–refeeding cycles. Similarly to the predictions of the model, these generally find a positive correlation between hormone concentrations in plasma and the amount of food eaten by the fish (Lescroart et al., 1998; MacKenzie et al., 1998; Power et al., 2000; Toguyeni et al., 1996; Van der Geyten et al., 1998) or mammal (Herwig et al., 2008; Lartey et al., 2015; Nillni, 2010). Adaptive regulation of growth processes is indicated by the often-observed positive relation between ration size and growth rate in short-time experiments, e.g. in tilapia (Dong et al., 2015; Fox et al., 2010; Toguyeni et al., 1996), white sturgeon (*Acipenser transmontanus*) (Cui et al., 1996), gilthead sea bream (*Sparus aurata*) (Bermejo-Nogales et al., 2011), cod (Berg and Albert, 2003) and polar cod (*Boreogadus saida*) (Hop et al., 1997). Food availability is suggested to be one of the most important environmental factors influencing growth rates in fish (Dmitriew, 2011; Enberg et al., 2012; MacKenzie et al., 1998). We have not been able to find studies following hormone levels and growth rates of animals on differently sized rations throughout their growth phase.

Higher food availability in the model habitats resulted in higher optimal GHF levels and thus higher growth rates. Even if GHF in the model is a simplified version of the GH–IGF-1 axis, its response to stimuli like food availability resembles results from empirical studies. These studies show that concentrations of insulin-like growth factor-1 (IGF-1), a mediator of GH, decreased when food was less available (Bermejo-Nogales et al., 2011; Fox et al., 2010; Lescroart et al., 1998). Even though both GH and IGF-1 are essential for growth in natural individuals, growth rate typically exhibits positive correlations with IGF-1 but not with GH (see below). In addition to promoting growth in natural fish, GH has a lipolytic effect, amplifying the use of reserves during times of food restriction (Jönsson and Björnsson, 2002). In the model, we assumed stable environments and thus conflated the multiple effects of GH to a single effect on growth, thus, the lipolytic effect of GH cannot arise as a GHF-effect but would need to be prescribed through explicit assumptions. If the model were analysed in variable environments, we expect that it would be adaptive to build reserves, and if so, a lipolytic effect could emerge through a combination of GHF and OXF.

Increasing food availability in the environment triggered high growth rates via a combined effect of THF and GHF, although THF had no direct effect on growth in the model. Empirical studies account for the effect of hormones from both hormone axes on

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growth, which makes the emergent correlation in THF and GHF levels plausible. Somatic growth depends on several different processes, including bone and muscle growth, which in turn combine processes regulated by hormones such as T_3 and IGF-1 from the two hormone functions. A study on tilapia documented a correlation between T_3 and specific growth rates (Toguyeni et al., 1996). In mammals, T_3 is involved in maintenance of chondrocytes and osteoblasts (Waung et al., 2012). It may have a direct effect on bone growth by local conversion and binding to thyroid receptors or an indirect effect via GH and IGF-1 (Nilsson et al., 2005). The interplay of TH and GH is also seen in chondrocyte development, in which a first phase is triggered by IGF-1 while the second phase depends on T_3 (Robson et al., 2002). The GH dynamics follow the Dual Effector Theory, in which GH can act directly on cells or indirectly via IGF-1 (Jönsson and Björnsson, 2002). Despite their actions taking place at different locations in the bones or cells, or at different times during bone maturation, bones cannot grow if one of the hormones is missing. IGF-1 also plays an important role in muscle growth (Dai et al., 2015; Grossman et al., 1997), but to our knowledge effects of thyroid on muscle growth have not been documented.

Achieving high growth rate is always related to an increased demand for energy. This demand can be met by changes in energy acquisition and allocation, and in the model we saw that energy acquisition was higher in environments where food was more accessible (Fig. 3). Optimally, roughly a third of intake was allocated directly to growth while the remainder was lost to other metabolic costs on the way (Fig. 3B). The calculated average for six different teleost fish allocating metabolizable energy to growth at maximum rations of food was about 40% (Cui and Liu, 1990). Minimum and maximum allocation rates were 21.3% and 63.4%, respectively. Thus, the optimal allocation rate found in this model is within the observed range.

In many freshwater and marine systems, predation risk decreases with body mass (Barnes et al., 2010; Zaret, 1980), putting a high reward on fast growth for young individuals. From a life history perspective one would expect a decrease in length growth as the individual gets larger, due to fewer potential predators for larger fish (Byström et al., 2015; Persson et al., 1996) and how the increased survival prospects lead to slower optimal growth that put more weight on survival and the future. However, larger fish are more efficient feeders because they are less exposed to risk when they are foraging (Claireaux et al., 2018), countering the first effect. These two opposing forces explain the rather linear growth seen in the predicted juvenile growth from this model, an observation also seen in other adaptive models for the ontogeny of growth when acquisition is flexible (Claireaux et al., 2018; Jørgensen and Holt, 2013).

The challenges for the internal regulation mechanisms concerning storage of energy depend on the past, current and expected food environment. In natural environments, this can include preparing for environmental change by storing energy in reserves. In a stable food environment as in our model, building a reserve is not necessary and because it involves costs, it never becomes optimal and there will be no variation in condition factor among individuals. A modelling approach analysing energy allocation in environments varying in food availability (Fischer et al., 2011) concluded that energy storage can be advantageous, but depends on the size of current reserves and how variable the environment is. An empirical study of more than 40 fish species or genera found that fish in stable habitats often have lower condition factors than fish in more unstable habitats (Fonseca and Cabral, 2007). This supports the fact that fish from the completely stable model environment have minimal reserves.

As preparation for foraging, orexin A pathways are activated when food gets scarce, while in the model impacts of OXF on intake are strongest in rich environments. In the model, we saw a positive correlation between food availability and optimal OXF levels. Due to easily accessible energy in rich environments it was optimal to invest more into growth. This created a higher energy demand in the model fish, which was met by increasing OXF levels and foraging activity. From empirical studies, orexin A is known to affect the individual's energy budget on a short-time scale. It is negatively correlated to leptin, which serves as a proxy for the amount of stored energy in adipose tissue. Food restriction can result in higher orexin mRNA production, orexin receptor and neuron activity (Rodgers et al., 2002). This is also the case for ghrelin, acting together with orexin to prepare for and initiate foraging (Matsuda et al., 2011; Miura et al., 2007). Under fasting conditions, ghrelin levels can increase (Iwakura et al., 2015; Jönsson, 2013). Despite the trigger, low levels of stored energy, being the same in experiments and the model, the context in which the trigger occurs is different. This results in high levels of orexin A and OXF at different food abundances.

The shift described in our model cascaded from endocrinal changes affecting energy allocation and acquisition, oxygen budgets, growth and mortality risk, which in total caused a concerted response towards more rapid growth in rich food environments. Comparing poor to rich food environments, higher growth rates were supported by THF levels that upregulated SMR and increased maximum oxygen uptake. A positive correlation between metabolic rate and a range of traits contributing to rapid growth rate was found in Trinidadian guppies (*Poecilia reticulata*) (Auer et al., 2018), and this was also the case for our model fish.

Shorter growth periods with higher growth rates in rich food environments resulted in higher survival. Besides supporting growth, high GHF levels contributed to reducing size-dependent mortality by growing out of vulnerable size windows more quickly. High THF levels also lowered mortality by making escape once predators were encountered more likely to be successful. Thus, total mortality experienced through the growth phase was lower and survival at the end of the growth phase increased. To our knowledge, only GH excretion has been linked to mortality in empirical studies. The special interest assigned to GH is probably due to husbandry in which several land-living and aquatic animals have been genetically modified to excrete more GH and thus could grow faster to slaughtering size, e.g. coho salmon (*Oncorhynchus kisutch*) (Raven et al., 2008) and pig (Ju et al., 2015). Several studies have been conducted with both transgenic and hormone-implanted trout and coho salmon. Even if salmon fry can experience lower survival in the presence of predators (Sundström et al., 2005), several studies have found that fish treated with GH, thus having higher growth rates, have mortality rates similar to non-treated fish (Johnsson and Björnsson, 2001; Johnsson et al., 1999; Sundström and Devlin, 2011). In our model, these effects would come about because GH increased the demand for food, and the resulting increase in appetite and foraging involved risk-taking that elevated mortality rates.

The selection of fast-growing individuals over several generations may also influence endocrinology, as seen in salmon (Fleming et al., 2002). A better understanding of the combination of endocrinology and its consequences for growth is relevant also for animal breeding programs, including fish farming. Many physiological processes and traits are linked by the endocrinal network. Selecting one of those traits will inevitably lead to changes in the endocrinal network and affect other traits. For example,

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selection for high growth rates could increase oxygen use in metabolic processes to a level where fish cannot sustain other metabolic processes simultaneously, something that can be described as a limited ability to multitask physiologically. This means that the majority of available oxygen is used for metabolic processes supporting growth, while little or no oxygen is left to assure free scope as would be required for predator escape in the model. Other processes not modelled, like immune function, could suffer from constraints on oxygen uptake and use. A study on first-feeding salmon fry showed increases in mortality for GH-transgenic individuals under natural conditions (Sundström et al., 2004).

This model is a first step towards combining internal and external control of appetite with energy allocation, growth and survival in teleost fishes. To reflect mechanisms in nature, McNamara and Houston (2009) argue that models should consist of complex environments and simplified organisms. In our case, the environment is simple while the animal model is complex. Even with this simple one-factor environment, we saw a gradual change in optimal strategies for hormone expression that resulted in concerted trait differences between populations in poor and rich habitats. The model suggests an adaptive interplay of hormone functions, where GHF, OXF and THF act together to cause an adaptive life history strategy that balances growth and survival throughout the juvenile phase. Often, effects of the internal control by means of hormones have been studied in isolation from the selection pressure of the external environment. For the future, we suggest it is not sufficient to study only how hormones carry signals from tissues and sensory organs to control centres like the hypothalamus, nor only how the control centre influences the decision processes in the body at many levels. Rather, there is a need to view the entire organism as an evolved system, where key hormones mirror internal states and respond to external factors. Such decisions concern growth and survival, as in this study, but also other life history traits linked to maturation time or physiological preparations for maturation. It is this combination of emphasis on the endocrinal network in the model fish and its impacts on ultimate mechanisms such as growth and survival that is characteristic of the model. It makes the model a tool for understanding processes and mechanisms underlying adaptations of growth. We think this is a fruitful path where many studies may follow.

MATERIALS AND METHODS

Simplifying the hormone systems for model implementation

The central challenge for our model organism is to grow and survive up to adult size. Although a high number of hormonal molecules and mechanisms are used to dynamically control physiology and behaviour in natural fish, we single out three clusters: growth, energy acquisition and overall metabolism. We will refer to them as 'functions' to distinguish them from real molecules and complex pathways involved. When combined in a life history model, these functions also determine energy allocation to reserves. The main components of our mode are thus the GHF, the ORF and the THF. Leptin also plays a role as it contains information about the individual's energy reserves. Below we describe the main hormones involved in these axes and our rationale for simplification.

Decisions connected to growth influence the individual's life history. For example, fast growth enables organisms to reach sexual maturity relatively early in their lives and start reproducing before conspecifics. Growth processes can make up a major part of energy use. The main endocrinal driver of growth in fish and mammals is GH and its associated hormone cascade (Björnsson, 1997; Jönsson and Björnsson, 2002). Thus, in terms of 'by-demand bioenergetics', GH drives the fish towards sizes at which they can mature and reproduce, implying that fitness considerations have set up an energy-demand that the organism needs to fulfil.

Part of the growth processes initiated by the secretion of GH is the accretion of proteins and breakdown of lipids. Both processes influence the individual's condition, and they increase metabolism. To maintain its condition, the individual must increase its energy uptake through foraging. Appetite and the initiation of feeding behaviour are very complex processes, comprising the central nervous system and peripheral signals. An important group of neuropeptides are orexins, as they are produced in the hypothalamus where signals on condition and energy budget are integrated. Thus, orexins are the second step in the physiological response of the 'by-demand bioenergetics' model, as they regulate the individual's energy acquisition in order to fulfil the growth goal set by GH.

To achieve growth, GH as initiator and orexin as energy-suppliant are important factors influencing growth rate. Diving into growth mechanisms, there is another hormone and its associated cascade being ubiquitous for growth to happen: TH. Hormones from the GH cascade and the TH cascade make up a complicated network in which they promote each other's secretion, conversion, receptor activity and, in a chronological order, the developments of both cartilage and bone (Cabello and Wrutniak, 1989; Robson et al., 2002). Another reason for implementing a function on THs is their regulating effect on metabolism (see below). On the one hand, an upregulated metabolism may be an advantage when energy is abundant. This would push the individual into a state of high energy turnover. On the other hand, any increase in foraging exposes the individual to a trade-off between energy provisioning and foraging-related risk. The increased metabolism due to THs may weaken this trade-off by allowing for faster metabolism and higher potential activity level, in turn causing higher ability to escape in case of a predator attack. In terms of the 'by-demand bioenergetics' model, the individual's performance to fulfil the set growth goal is improved by higher energy turnover and oxygen uptake rates when conditions allow.

Starting with empirical data on stimuli, hormone regulation and effects, we now present the functions and mechanisms of these three clusters. Thereafter we will use this as background for the implementation in model code.

The GHF

Effects

GH is expressed throughout life. In humans, maximal secretion is seen during puberty, then decreasing with age (Vermeulen, 2002; Zadik et al., 1985). GH seems to affect metabolism and body composition (Vélez et al., 2019; Vermeulen, 2002; Yang et al., 2018), but main effects are directed towards growth in bone (Nilsson et al., 2005; Robson et al., 2002) and muscles (Grossman et al., 1997). For fish, a relationship between GH levels and compensatory growth is suggested (Ali et al., 2003). To some extent GH also influences behaviour, either in a direct or indirect way (Jönsson and Björnsson, 2002). As growth rates can be constrained by environmental factors such as food availability, one would expect that GH levels and levels of its mediator IGF-1 fluctuate in line with seasonal variation. Any increase in GH-regulated growth processes depends on stimuli, e.g. information on the individual's current energetic status. In times of high food availability and increasing reserves, it is expected that individuals invest in growth as energy is relatively easily available. Food availability often varies predictably, for example algal blooms or increased vegetation in spring in temperate zones. Fluctuations, which might be stimulated by changes in photoperiod have been observed in reindeer (*Rangifer tarandus*) (Suttie et al., 1991, 1993) and Arctic char (*Salvelinus alpinus*) (Jørgensen and Johnsen, 2014).

Axis

GH production is controlled by a hormonal cascade, the somatotrophic axis. On top, GH-releasing factor (GRF) and/or somatostatin (SRIF) are released by the hypothalamus upon environmental or peripheral stimuli. These regulate the anterior pituitary activity, which alters the rate of GH secretion. GH effects are mediated by IGF-1 in most tissues. Both GH and IGF-1 can affect mechanisms in target tissues (Gatford et al., 1998; Peter and Marchant, 1995).

Stimuli

Through evolution the number of factors regulating GH release has decreased, while it is multifactorial in fish, regulation in mammals is

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mostly achieved by a 'dual-control system' (Gahete et al., 2009). The mammalian system consists of one main stimulator, growth hormone-releasing hormone (GHRH), and one main inhibitor, somatostatin (SRIF). Additional stimulators of minor importance are neuropeptide Y (NPY), ghrelin, exercise, and in some species leptin (Gahete et al., 2009; Hamrick and Ferrari, 2008; Kojima et al., 1999; Lanfranco et al., 2003). Leptin signals the current reserve size (Cammisotto and Bendayan, 2007), while ghrelin prepares the digestive tract for incoming food (Müller et al., 2015). In fish, a second main stimulator is pituitary adenylate cyclase-activating polypeptide (PACAP). Additional weaker stimuli come from thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH) and others. Leptin does not exert a direct stimulus in fish (Gahete et al., 2009).

Melatonin (Suttie et al., 1992, 1991) regulates IGF-1 secretion. It is important to notice that one stimulus can have different effects on GH and IGF-1. This is for example the case in a study on fasted tilapia (*Oreochromis mossambicus*), where both body growth rates and body weight in males decreased due to fasting. IGF-1 levels correlated with growth rates, but GH levels were unchanged. A possible explanation is that available energy is used to cover basal metabolism first, while hormone levels are adapted to reduce or cease growth (Uchida et al., 2003). This is also the case for a diet experiment with Arctic char. Concentrations of GH did not reflect changes in body weight, but IGF-1 concentrations did (Cameron et al., 2007). Unchanged or even elevated levels of GH can be part of a fasting response in which GH impels lipolysis and prevents protein degradation (Richmond et al., 2010).

Inhibition of GH is also exerted via IGF-1 in a long feedback loop in both fish and mammals (Gahete et al., 2009).

The OXF

Effects

Orexin is a neuropeptide known from humans (Kalamatianos et al., 2014; Oka et al., 2004; Tomasik et al., 2004), pigs (Kaminski et al., 2013), rats (Dube et al., 1999) and fish (Facciolo et al., 2010). There are two types of orexin, A and B, which have several effects, including feeding-related and behavioural effects (Cai et al., 2002; Rodgers et al., 2002). Orexin A stimulates foraging in goldfish (*Carassius auratus*) (Volkoff et al., 1999) and rats (Dube et al., 1999; Rodgers et al., 2000). Positive correlations between caloric demand and both orexin A and B exist for children (Tomasik et al., 2004). Observations of mice injected with orexin A and B revealed no effect of orexin B on food intake, while orexin A increased food intake and metabolism (Lubkin and Stricker-Krongrad, 1998). One mechanism by which orexin can act on food intake is via regions in the brain such as the arcuate nucleus (ARC) (Rodgers et al., 2002), where also leptin influences energetic processes in the body. It has also been suggested that foraging activity is increased by delaying satiety, as shown for low-dose treatments in rats (Rodgers et al., 2000). Effects not related to feeding include a general arousal, reduced pain perception, increased locomotion, etc. (Rodgers et al., 2002), and many of these can be seen as enabling for foraging. Despite both orexins being present in a variety of organisms, the effect of orexin A on feeding behaviour seems to be much stronger than that of orexin B (Edwards et al., 1999; Haynes et al., 1999; Nakamachi et al., 2006; Sakurai et al., 1998). Beside the direct influence of orexin neurons by leptin via leptin receptors (Funahashi et al., 2000; Sakurai, 1999), orexin neurons are also influenced by neurons responsive to NPY and Agouti-related peptide (AgRP) (Sakurai, 1999). NPY/AgRP-neurons are of first-order, thus they collect incoming information on the individual's energetic status and translate this information into a downstream response (Barsh and Schwartz, 2002; Loh et al., 2015).

Stimuli

Factors influencing the secretion of orexin describe the body's current state in terms of energy availability. A stimulating factor reported for rats is the fall in plasma glucose levels, eventually in combination with an empty stomach (Cai et al., 2002, 1999). However, a study on rats with insulin-induced fall in plasma glucose only showed an increase in hypothalamic orexin B (Cai et al., 2001). When energy is available to the organism, orexin secretion is inhibited. A signal of ingested food can be gastric distension (Cai et al., 1999). Leptin receptors have been found linked to orexin neurons in rodents and primates (Horvath et al., 1999) and may decrease the secretion of orexin in the hypothalamus (Kalra et al., 1999). Orexin A is believed to be part of a short-term response to ensure energy balance in the body (Cai et al., 1999; Rodgers et al., 2002).

Orexin effects in fish are similar to those in mammals (Matsuda et al., 2012) and they have been detected in several fish species (Miura et al., 2007; Nakamachi et al., 2006; Volkoff et al., 2003). Most experiments are done on goldfish (Penney and Volkoff, 2014), but also cavefish (*Astyanax fasciatus mexicanus*) show an increase of orexin A in relation to food intake (Penney and Volkoff, 2014). An interplay between orexin and ghrelin is suggested for foraging initialisation, in which ghrelin stimulates food intake and mediates orexin effects (Miura et al., 2007; Penney and Volkoff, 2014). Ghrelin is known from several fish species (Matsuda et al., 2011). In mammals, an increase in ghrelin-concentrations can be observed before food intake (Müller et al., 2015). In fish, it seems that patterns in ghrelin secretion are more species-specific. Several species show increases, as in mammals, but also decreasing concentrations are found (Jönsson, 2013; Penney and Volkoff, 2014; Rønnestad et al., 2017). Despite differing mechanisms, it seems that the positive effect of ghrelin on foraging is similar across fish species. In addition to direct effects on feeding, orexin also exerts effects on other behaviours, like waking and locomotion (Rodgers et al., 2002). Its comprehensive effects are supported by the widespread presence of orexin receptors in the brain (Sakurai, 1999).

The THF

Effects

In mammals and fish, THs are major factors regulating metabolism and development. The hormones affect brain development (Di Liegro, 2008), metamorphosis (Youson et al., 1994) and, in combination with GH, bone growth (Nilsson et al., 2005; Robson et al., 2002). Throughout life the basal metabolic rate is regulated by TH (Heilbronn et al., 2006; Herwig et al., 2008; Kitano et al., 2010; Webb, 2004). Due to their effect on metabolism they also play an important role in preparing organisms for seasons of low temperature and food availability [e.g. in red deer (*Cervus elaphus*) (Kuba et al., 2015), red knot (*Calidris canutus canutus*) (Jenni-Eiermann et al., 2002), reindeer (Bubenik et al., 1998) and white grouper (*Epinephelus aeneus*) (Abbas et al., 2012)]. Consequently, some seasonal variation in circulating hormone levels can be detected. A reduction of up to 30% in basal metabolic rate in the absence of TH is documented for endotherms, and this reduction can be linked to thermogenesis (Heilbronn et al., 2006; Mullur et al., 2014; Silva, 2003). Non-thermogenic effects include the regulation of body weight and metabolism of triglycerides and carbohydrates (Mullur et al., 2014; Varghese and Oommen, 1999; Varghese et al., 2001). In both mammals and fish, an impact on cardiac output is documented (Carr and Kranias, 2002; Little and Seebacher, 2014), and effects of TH on resting hearts have been shown in zebrafish (*Danio rerio*) (Little and Seebacher, 2014). As cardiac output contributes to maintain aerobic scope, TH also impacts the animal's ability to sustain sufficient oxygen uptake under changing temperatures (Little and Seebacher, 2014).

Axis

TH secretion depends on a hormone cascade sustaining relatively constant circulating hormone levels. On environmental or peripheral stimulation, TRH is secreted by neurons in the hypothalamus. In mammals, it promotes release of thyroid-stimulating hormone (TSH) from the pituitary. In fish, the relation between TRH and TSH is not as clearly defined (Abbott and Volkoff, 2011; Chatterjee et al., 2001). In both mammals and fish, TSH acts on the thyroid gland, the actual place of TH production, which is stimulated to release TH into the blood. Those are mainly thyroxine (T_4) but also triiodothyronine (T_3), which differ in the number of their iodide ions (Han et al., 2004; Zoeller et al., 2007). Relatively constant hormone levels in the body are accomplished by negative feedbacks in the hormone cascade (Fekete and Lechan, 2014; Zoeller et al., 2007). TH are mainly eliminated from the blood by deiodination in the liver (Malik and Hodgson, 2002; Zoeller et al., 2007). The first deiodination-process forms the bioactive T_3

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from T_4. There is also some evidence on the direct effect of TRH on feeding and locomotor activity (Abbott and Volkoff, 2011).

Target tissues, such as the brain, bones and kidneys, contain different kinds of metabolic enzymes, deiodinases, to remove iodide from the hormones (Friesema et al., 1999; Miura et al., 2002). Biologically inactive T_4 has to be converted to T_3 in order to have an effect on tissues (Zoeller et al., 2007). There are three deiodinases, which successively can remove iodide ions to form T_3, T_2 and T_1. An inactive form called reverseT_3 can also be produced (Zoeller et al., 2007). Although it seems that most studies are concerned with the actions of T_3, there is some evidence on effects of T_2 (Lanni et al., 2001) and T_4 (Robson et al., 2002).

Stimuli

Several factors stimulating the release of TH have been identified, e.g. leptin (Abel et al., 2001; Herwig et al., 2008; Nillni et al., 2000) and insulin (Lartey et al., 2015). Leptin transfers information based on individual fat stores to the brain (Cammisotto and Bendayan, 2007) where the signal influences secretion of TRH positively (Fekete and Lechan, 2014). Inhibiting effects are known from stress (Silberman et al., 2002), exhaustive exercise (Hackney and Dobridge, 2009) and melatonin (Ikegami and Yoshimura, 2013; Ono et al., 2008).

Simplification of hormones functions in the model

GHF

As our interest is in hormone strategies for growth, the GH cascade is reduced to one variable in the model. This is a proxy for a fish's IGF-1 blood plasma concentration and regulates the amount of energy drained from reserves and used for building all kinds of somatic structures, including bones. The complex hormonal network of ghrelin, leptin and the somatotrophic axis is resembled in the interaction of GH and current body states, notably energy reserves and satiety. In the model the axis, its effects and stimuli are referred to as the GHF (Eales, 1988).

OXF

The OXF represents stimuli, hormone secretion and effects of orexin as one value. For the model, only orexin A is regarded. To simplify its effects, the OXF only affects foraging behaviour in a positive manner. Foraging is assumed to include a series of other effects, such as arousal and increased locomotion, and in the model these are reflected in energetic foraging costs. Motivated from behavioural ecology, there comes a mortality cost with increasing foraging activity as looking for food involves potential encounters with predators. In the model we consider the longer-term effect of the ORF as a proxy for the mean orexin A concentration in the body during this period of time. Orexin A concentrations vary on a timescale much shorter than the time resolution chosen here. For example, concentrations can vary with a daily cycle (Grady et al., 2006), and furthermore during the oestrous cycle (Kaminski et al., 2013), body weight reduction (Bronsky et al., 2007) and prepro-orexin mRNA increases in fasting individuals (Cai et al., 1999). Here we concentrate on the mean effect orexin A has on stimulating foraging activity over the course of one model time step.

THF

For the purpose of the model, a long-term effect of TH is of interest. Stress from predation, insulin and other factors that signal environmental or individual conditions on a short timescale are hence neglected. In the model the thyroid cascade is reduced to a simple factor resembling blood concentrations of bioactive T_3. Negative feedback and elimination in order to receive relatively constant concentrations of TH in the body are disregarded; this is also done for the minor effect of T_2 and T_4. Effects of TH are reduced to an influence of thyroid on metabolism. Metabolism is regarded as the mean turnover of energy from food to reserves, soma or activities. The influence of TH on metabolic mechanisms in the model is summarized in a positive linear correlation between TH concentration and SMR. While this correlation is regarded as the cost of TH, a benefit comes with the positive linear correlation between TH and potential oxygen uptake, for example partly mediated through heart function. An increase in potential oxygen uptake (caused by TH) results in a greater free aerobic scope, which in turn contributes to better swimming ability and higher escape probability in case of a predator attack. Non-metabolic processes such as brain development or metamorphosis are not part of the model. As the 'thyroid axis' in the model covers response to stimuli, the hormones themselves and their effects, it is called THF (Eales, 1988).

Leptin is not modelled directly, but signals size of the energy reserve and therefore allows the model to have a reserve as an individual state that can potentially influence the levels of the other hormone functions.

Model description

Hormones regulate physiological and behavioural processes, and these in turn achieve benefits and incur costs that may depend on the environmental conditions and the state of the organism. When we say we model hormones, it is therefore the effects of hormones that are in focus, in our case their consequences for growth and survival of juvenile fish. We first give the four central equations that describe growth and survival in our model, then detail the underlying processes. Throughout, capital letters are used for array variables that describe the organism and may change over time or with state (listed in Table S2), while lowercase is used for parameters that have a specific value (listed in Table S1). Greek letters denote the strategies, i.e. the hormone levels that the model optimizes. Central aspects of energetics, oxygen use and hormonal regulation are visualized in Fig. 1.

The model characterizes fish body mass W [g] as being separated into two components, where the structural body mass $W_{\text{structure}}$ [g] grows irreversibly. On top of that are the energy reserves R [J] that can be built or tapped, having an energy density d_{reserves} [J g^{-1}]:

$$W = W_{\text{structure}} + \frac{R}{d_{\text{reserves}}}. \quad (1)$$

The distinction between irreversible structure and dynamic reserves is common for many models, including DEB (Kooijman, 2010). Growth $\Delta W_{\text{structure}}$ [g week^{-1}], the irreversible increase in structural body mass, depends on the level γ [ng ml^{-1}] of the GHF relative to its maximum value $\gamma_{\max}$ [ng ml^{-1}], current structural weight and k_{growth} [week^{-1}], which sets the upper limit for proportional increase in structural body mass per time step (weeks):

$$\Delta W_{\text{structure}} = \frac{\gamma}{\gamma_{\max}} \cdot k_{\text{growth}} \cdot W_{\text{structure}}. \quad (2)$$

From the bioenergetics budget it follows that all energy taken up as food I [J min^{-1}] is used for either metabolic processes P [J min^{-1}] or to pay energetic costs of building tissues C [J min^{-1}]. These new tissues include both new soma and changes in reserves:

$$I = P + C. \quad (3)$$

The details of I, P and C are described in detail further down. Hormonally, I is controlled by the OXF, C by the GHF through tissue costs of growth and P is influenced by the extra metabolic costs of expressing the THF.

The last central equation relates to survival probability S [week^{-1}], which is given by S=e$^{-M/52}$ where M [year^{-1}] is the total mortality rate compounded by several components:

$$M = m_{\text{fixed}} + M_{\text{size}} + M_{\text{foraging}} + M_{\text{scope}} + M_{\text{foraging}\times\text{scope}}. \quad (4)$$

Here m_{fixed} is a constant irrespective of size, state or strategy. M_{size} is a predation rate that declines with size. M_{foraging} is predation resulting from exposure while foraging. M_{scope} is increased vulnerability when the individual's overall metabolic rate is close to its maximum aerobic capacity, because it is then harder to escape an attack. Similarly, $M_{\text{foraging}\times\text{scope}}$ is extra mortality when the individual exposes itself to predators while it is exhausted, which would put it in double jeopardy. The THF affects both M_{scope} and $M_{\text{foraging}\times\text{scope}}$.

Understanding the model requires that the equations above are interpreted in light of three key trade-offs that we describe here and give details and equations for further down.

First, the energy requirement of growth and everything else has to be met by foraging for food, which involves taking some level of extra risk (Krause

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and Godin, 1996; Lima and Dill, 1990; Sih, 1992). A resting fish often seeks safety in a shelter but needs to leave this to seek habitats where prey, and most often predators, are more common. Acquisition of more food thus involves more encounters with predators, and when food is scarce the fish needs to search for longer and expose itself more to forage the same amount.

Second, aquatic breathing is rapidly limited by surface-to-volume ratios and gas diffusion, even for small organisms. Although respiratory organs such as gills have evolved to overcome these constraints, there are physical limits to permissible total metabolic rate (Priede, 1985). Maximum aerobic capacity is often measured on fish that swim in respirometers, but digestion and growth are also variable processes that contribute to total metabolic rate. When the overall level of metabolic processes requires a lot of oxygen, the fish is quickly exhausted and therefore less efficient at evading predators should it encounter one.

Third, a trade-off that has received less attention is how spending energy can help an organism to manage, mitigate or reduce risk. It is known that immune systems incur energetic costs, and that the optimal level of immune function depends on energetic status, the risk of infections and availability of resources. Here we use thyroid regulation of metabolic level to achieve a similar exchange between energy and risk. The model assumes metabolic level can be upregulated by thyroid at an energetic cost (subject to trade-off 1), and the extra metabolic capacity is modelled as an elevated aerobic scope (alleviating trade-off 2). Consequently, the model allows metabolic rate to vary systematically between ecological settings.

We use a state-dependent model to find the optimal hormonal control of acquisition and allocation of energy. This type of mechanistic model finds the evolutionary endpoint (beyond which further changes cannot improve fitness) for a given environment. The model first uses dynamic programming (Clark and Mangel, 2000; Houston and McNamara, 1999) to find the optimal hormone expression for each combination of the individual's states. This is referred to as the strategy, as it contains information about what the individual optimally should do under each circumstance and in each state. The individual states included are the body length of the fish and its energy reserves. Thereafter, an individual that makes use of the optimal strategy according to its current individual state is simulated. We record its trajectory of growth, physiology, behaviour and risk-taking to quantify and analyse effects. The model optimizes the state-dependent trajectory of the three hormones (GHF, OXF and THF) by maximizing juvenile survival between 10 cm and 30 cm body length. The time steps are set to one week to represent typical dynamics of hormone levels and growth processes, which means that more rapid processes like behaviours are not modelled in minute-to-minute detail but for their cumulative effects at a weekly scale. The model describes growth of a juvenile fish in environments with constant food availability, and we compare several different environments in our analyses.

Energy budgets and metabolic rate

The total metabolic rate P [J min^{-1}] is the sum of all respiratory processes, all with unit joules:

$$P = P_{\mathrm{SMR}} + P_{\mathrm{foraging}} + P_{\mathrm{SDA}} + P_{\mathrm{reserves}} + P_{\mathrm{growth}}. \quad (5)$$

Here P_{SMR} [J min^{-1}] is the standard metabolic rate, P_{foraging} [J min^{-1}] the swimming cost of foraging behaviour, P_{SDA} [J min^{-1}] the cost of digestion and energy uptake (SDA) until the resources are available in the bloodstream, and P_{reserves} [J min^{-1}] and P_{growth} [J min^{-1}] the metabolic costs of converting between resources in the bloodstream and reserve and structural tissue, respectively.

On top of that, the organism uses its digested resources for incorporation as new structural tissue (C_{growth} [J]) or by adding to or using from energy reserves (ΔR [J]). The net rate C [J min^{-1}] of such incorporation of energy into tissue is thus:

$$C = (C_{\mathrm{growth}} + \Delta R)/k_{\mathrm{MinutesPerWeek}}. \quad (6)$$

Note that while P and C both contribute to the individual's energy budget (Eqn 3), only P uses oxygen through aerobic respiration (Eqn 24).

SMR scales allometrically with body mass as the fish grow from juvenile to adult size. Other contributors to an individual's overall metabolic rate are factors like locomotion, digestion and growth, and many of these may change with ontogeny (Mozsár et al., 2015).

The model uses variants of SMR in several ways. What is measured experimentally as SMR and that we refer to as P_{SMR} is the standard oxygen consumption of the organism's total body mass as it is affected by the level of the THF. We first consider the baseline level of SMR at a mean level of THF expression as:

$$P_{\mathrm{standard}} = k_{\mathrm{SMR}} \cdot W^{a}. \quad (7)$$

Here, k_{SMR} has unit [J min^{-1} g^{-a}]. P_{standard} can be up or downregulated under the influence of THF, modelled as the concentration τ [ng ml^{-1}] and relatively to a maximum concentration τ_{max} [ng ml^{-1}]:

$$P_{\mathrm{SMR}} = \left[1 + \left(\frac{\tau}{\tau_{\mathrm{max}}} - 0.5\right) \cdot k_{\mathrm{THF\_SMR}}\right] \cdot P_{\mathrm{standard}}. \quad (8)$$

Here, $k_{\mathrm{THF\_SMR}}$ determines the strength of the effect of THF on metabolic rate, or in other words, the energetic cost of upregulating the scope for metabolic activity. It is P_{SMR} that enters the individual's metabolic rate (Eqn 5).

When we model food intake as a multiple of SMR, it is unlikely that a chubby individual has higher foraging success per time and energy investment compared to a leaner fish, so we scale food intake with $P_{\mathrm{structure}}$, a measure of SMR calculated from the lean body mass only and not affected by THF:

$$P_{\mathrm{structure}} = k_{\mathrm{SMR}} \cdot (W^{a}_{\mathrm{structure}}). \quad (9)$$

Foraging and digestion

Energy from foraging is ultimately used to drive all energy-dependent processes in the organism. We model foraging as controlled by appetite through the OXF where the relative concentration of OXF ($\alpha/\alpha_{\mathrm{max}}$) is proportional to the target intake rate I of the individual, which is expressed as:

$$I = \frac{\alpha}{\alpha_{\mathrm{max}}} \cdot k_{\mathrm{OXF}} \cdot P_{\mathrm{structure}}. \quad (10)$$

Intake I [J min^{-1}] is defined as metabolizable energy absorbed by the gut; urinary and fecal loss of energy are implicitly included in the dimensionless coefficient k_{OXF} (Bureau et al., 2003). Here $P_{\mathrm{structure}}$ is a standardized metabolic rate of the lean body mass, explained in Eqn 9 above, used because it is unrealistic that having large reserves contributes to more efficient foraging.

The foraging behaviour $B_{\mathrm{forgaging}}$ [dimensionless, given in multiples of $P_{\mathrm{structure}}$] required to meet the energetic demand depends on food availability in the environment. We first rescale foraging intake to multiples of SMR, which allows us to find the level of foraging behaviour needed to meet the orexin-regulated appetite in a certain food environment E [dimensionless]. We assume that food is quicker and safer to find in rich food environments:

$$B_{\mathrm{foraging}} = \frac{I}{P_{\mathrm{structure}} \cdot E}. \quad (11)$$

The cost of foraging activity (P_{foraging}) is proportional to foraging activity and SMR with a coefficient k_{foraging} [dimensionless]. Physical activity during foraging requires moving the whole body, including soma and reserves, so SMR is based on total weight.

$$P_{\mathrm{foraging}} = k_{\mathrm{foraging}} \cdot B_{\mathrm{foraging}} \cdot P_{\mathrm{standard}}. \quad (12)$$

Food eaten is processed by the digestive system and taken up into the bloodstream. Specific dynamic action SDA (P_{SDA}), representing the cost of digestion, is the product of intake and a constant k_{SDA} [dimensionless].

$$P_{\mathrm{SDA}} = k_{\mathrm{SDA}} \cdot I. \quad (13)$$

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Growth and reserves

Structural weight ($W_{structure}$) is calculated based on length L [cm] using Fulton's condition factor for lean fish ($k_{Fultons\_min}$, [0.01 g cm^{-3}]):

$$W_{structure} = k_{Fultons\_min} \cdot L^3. \quad (14)$$

Likewise, maximum storage depends on body size and is calculated from the difference between maximum ($k_{Fultons\_max}$, [0.01 g cm^{-3}]) and lean condition factor, and the energy density of the reserves ($d_{reserves}$, [J g^{-1}]):

$$R_{max} = d_{reserves} \cdot (k_{Fultons\_max} - k_{Fultons\_min}) \cdot L^3. \quad (15)$$

The cost of structural growth C_{growth} follows directly from the amount of new tissue produced (Eqn 2) and the somatic energy density $d_{structure}$ [J g^{-1}]:

$$C_{growth} = \Delta W_{structure} \cdot d_{structure}. \quad (16)$$

While reserves may vary in size, the model assumes that structural growth is irreversible ($C_{growth} \geq 0$). A breakdown of soma, e.g. muscle tissue during starvation as seen in nature, is thus restricted to the part included in the reserves.

To meet the requirements of different tissues, nutrients have to be converted, and conversion of metabolites comes with a cost. When storing energy, processing of nutrients into storage molecules is based on a conversion efficiency $k_{conversion\_reserves}$ [dimensionless]. The model assumes this conversion to be biochemical processes that requires oxygen and therefore will contribute to overall metabolic rate:

$$P_{reserves} = \Delta R(1 - k_{conversion\_reserves})/k_{MinutesPerWeek}, \quad \text{if } \Delta R \geq 0. \quad (17)$$

If energetic expenses exceed the energy available from digestion, reserves have to be drained. Then a conversion cost has to be paid for making those reserves accessible:

$$P_{reserves} = \frac{-\Delta R}{k_{conversion\_reserves}}(1 - k_{conversion\_reserves})/k_{MinutesPerWeek}, \quad \text{if } \Delta R < 0. \quad (18)$$

In the case of growth, metabolites are drawn from reserves and converted into building blocks. The cost P_{growth} of conversion into growth is also calculated using a conversion efficiency parameter $k_{conversion\_growth}$ [dimensionless]:

$$P_{growth} = \frac{C_{growth}}{k_{conversion\_growth}}(1 - k_{conversion\_growth})/k_{MinutesPerWeek}. \quad (19)$$

Aerobic scope

The maximum rate of oxygen uptake has to accommodate all oxygen-dependent processes such as digestion, locomotion, foraging, conversion of energy and other metabolic activities (Fry, 1971). We refer to the unused surplus as the free aerobic scope (Holt and Jørgensen, 2015).

We calculate potential oxygen uptake $A_{standard}$ [J min^{-1}] following Claireaux et al. (2000) as an allometric function with exponent $b<1$. Because it is unrealistic that variations in reserve size affect an individual's capacity for oxygen uptake, we base calculations of aerobic scope on the structural body mass only:

$$A_{standard} = k_{scope} \cdot (W_{structure}^b). \quad (20)$$

Here, k_{scope} has unit [J min^{-1} g^{-b}].

A key assumption of our model is that the THF increases aerobic scope through increasing capacity for oxygen uptake, thus permitting higher levels of metabolic processes, but at a cost on SMR (Eqn 8):

$$A_{max} = \left[1 + \left(\frac{\tau}{\tau_{max}} - 0.5\right) \cdot k_{THF\_scope}\right] \cdot A_{standard}. \quad (21)$$

Here, k_{THF_scope} [dimensionless] sets the strength of the effect of THF on increased scope.

Food availability

Across model runs we vary food availability, implemented as the factor E [dimensionless]. When food availability is good (high E), less foraging activity is required to obtain the given amount of resources (Eqn 11). Contrary, when E is low, the individual needs more time to gather the amount of food it aims for. Consequently, E, through $B_{foraging}$, determines the exposure to predators in Eqn 23, and the energetic cost of foraging in Eqn 12. In this version of the model, there is no stochasticity influencing foraging success.

Mortality rates

In this model, mortality is decompounded into discrete risk factors (Eqn 4) that through separate trade-offs contribute to an individual's risk of being depredated or otherwise die (extended from Holt and Jørgensen, 2014). All mortality rates (with capitalized M) are in unit year^{-1}, while the units of the various constants introduced (with small m) are given in Table S1. The first is a constant component m_{fixed} represents death due to causes that are independent of the individual's state or behaviour, e.g. some types of disease. Second is size-dependent mortality, with reduced risk of mortality with larger body size, as is both observed (Gislason et al., 2010; Peterson and Wroblewski, 1984) and resulting from the size-structure of marine food webs and scaling relationships (Brown et al., 2004). We model this as an allometric relationship with a negative exponent:

$$M_{size} = m_{size} \cdot L^{x_{size}}. \quad (22)$$

The next mortality component reflects the well-known trade-off between risk of predation and foraging intensity (e.g. Lima, 1998). The model assumes that individuals expose themselves to predation risk while foraging, and that this risk accelerates with increasing foraging because the safest habitats and time periods are assumed exploited first:

$$M_{foraging} = m_{foraging} \cdot M_{size} \cdot B_{foraging}^{x_{foraging}}. \quad (23)$$

For this and the risk components below, it is assumed that predation is the ultimate cause for death and therefore that the risk declines with size in the same way as the size-dependent predation mortality.

The final two components relate to oxygen use and aerobic scope, i.e. the difference between maximum oxygen uptake and actual rate of oxygen use. Fleeing from predators demands burst swimming, which is achieved anaerobically by white muscle (Johnston, 1981; Rome et al., 1988; Weber et al., 2016). Recovery is aerobic and faster if there is free aerobic scope to provide abundant oxygen (Killen et al., 2014; Marras et al., 2010), thus preparing the individual for a repeated attack or the next encounter. We model this based on the ratio between used and available oxygen, raised to a power to describe how predation risk increases rapidly as maximum oxygen uptake is approached or even temporarily exceeded:

$$M_{scope} = m_{scope} \cdot M_{size} \cdot \left(\frac{P}{A_{max}}\right)^{x_{scope}}. \quad (24)$$

The model finally assumes that it is particularly risky for an individual to expose itself (high $M_{foraging}$) when oxygen use is high (high M_{scope}) because attacks would be frequent and recovery at the same time slow:

$$M_{foraging \times scope} = m_{foraging \times scope} \cdot M_{foraging} \cdot M_{scope}. \quad (25)$$

The mortality rates [year^{-1}] stemming from each risk factor are then summed (Eqn 4) and survival per time step [week] given as $S = e^{-M/52}$.

Implementation

The model follows juvenile fish as they grow from 10 cm to 30 cm body length. Optimal solution is found for each combination of the individual states length (21 steps) and reserves (10 steps). Hormone levels are discretized into 160 each. Time step is 1 week, and we allow sufficient time horizon for all fish to reach maximum size, which normally takes less than 200 weeks for the slowest ones.

Parameterization

Parameters used in the model were chosen from different fish species to create a generalized, juvenile fish. Many of the studies used were performed on Atlantic cod, which makes cod the fish most similar to the model fish.

For orexin A no studies on hormone concentrations in fish are known. In this case measurements on mammals were used.

The water temperature was set constant at 5°C and water was assumed saturated with oxygen.

Energy density for reserves was chosen to be 5000 J/g. This is based on a calculation of mean protein and fat contents in storage tissues. A fish of 750 g served as a template. Energy density was based on the weight of liver and white muscle tissue and their proportional content of fat and proteins. For proteins, cellular water was taken into account.

Since growth requires development of more specialized tissue than storing molecules in reserves, the conversion efficiency for growth was set lower than for reserves.

Fulton's condition factors for fish with full reserves ($k_{\text{Fultons\_max}}$) and depleted reserves were chosen following a study on cod (Lambert and Dutil, 1997b).

Variables used in calculations of SMR (k_{SMR}, α) were based on Clarke and Johnston (1999), Mozsár et al. (2015) and Pangle and Sutton (2005), describing the resting metabolic rate of a general teleost fish. In line with earlier models built on a similar bioenergetics template (e.g. Jørgensen and Fiksen, 2010), we used a scaling exponent a=0.7, which is within the range of intraspecific scaling exponents among teleosts (Killen et al., 2007). Also, studies show that there is great variation in scaling exponents in animals and the value chosen here was in the range of this variation (Holdway and Beamish, 1984; Kjesbu et al., 1991; Lambert and Dutil, 1997a). Units were converted to fit the model.

The coefficient k_{scope} used in calculations was derived from a study on cod (Claireaux et al., 2000). The scaling exponent for aerobic scope (b) was chosen in accordance with SMR scaling (Holt and Jørgensen, 2014).

Hormone concentrations

Concentrations of IGF-1 were given in ng/ml blood plasma and the model allowed a range from 0–200. In experiments with tilapia concentrations of 70–120 ng/ml plasma were measured (Uchida et al., 2003). A study on Arctic char revealed concentrations up to approximately 250 ng/ml plasma (Cameron et al., 2007).

Orexin A has been detected in concentrations up to roughly 350 pg/ml porcine blood plasma (Kaminski et al., 2013), which is a range assumed to be normal for adult men and women (Oka et al., 2004). The range is higher for children, where measurements up to roughly 1300 pg/ml have been observed (Tomasik et al., 2004). The model allowed orexin A up to 2000 pg/ml blood plasma. Its existence and function in fish has mainly been documented in goldfish (Abbott and Volkoff, 2011; Hoskins et al., 2008; Volkoff et al., 1999) and zebrafish (Matsuda et al., 2012).

Concentrations of T_3 were given in ng/ml of blood plasma and range of 0–5. The range was chosen according to measurements on teleosts, e.g. 1-year-old rainbow trout (*Oncorhynchus mykiss*) (Eales, 1988), *Anabas testudineus* (Varghese and Oommen, 1999; Varghese et al., 2001) and chum salmon (*Oncorhynchus keta*) (Tagawa et al., 1994), which revealed concentrations up to roughly 4.5 ng/ml plasma for normal individuals.

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Competing interests

The authors declare no competing or financial interests.

Author contributions

Conceptualization: J.W., C.H.J., J.G., S.E., C.J.; Methodology: J.W., C.H.J., J.G., S.E., C.J.; Software: J.W., C.H.J., S.E., C.J.; Validation: J.W., C.H.J., J.G., S.E., C.J.; Formal analysis: J.W., C.H.J., J.G., S.E., C.J.; Investigation: J.W., C.H.J., J.G., S.E., C.J.; Resources: S.E.; Writing - original draft: J.W.; Writing - review & editing: J.W., C.H.J., J.G., S.E., C.J.; Visualization: J.W., C.H.J., J.G., S.E., C.J.; Supervision: J.G., S.E., C.J.; Project administration: S.E.; Funding acquisition: J.G.

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Data availability

Model code can be accessed from the Supplementary information (Tables S3 and S4) or from https://github.com/JacquelineWeidner/Hormonal-regulation-of-growth-in-juvenile-fish.git.

Supplementary information

Supplementary information available online at
http://bio.biologists.org/lookup/doi/10.1242/bio.046144.supplemental

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Table S1. Parameters used in the growth model of a generalized fish using hormonal strategies to adapt to environmental challenges.

Parameters				
Name	**Value**	**Unit**	**Definition**	**Literature**
a	0.7	-	Exponent for standard metabolic rate	(Clarke and Johnston, 1999)
b	0.7	-	Exponent for calculation of maximum aerobic scope	-
d_{reserves}	5 000	J g^{-1}	Energy density of reserves	-
$d_{\text{structure}}$	4 000	J g^{-1}	Energy density of soma	-
$k_{\text{conversion\_growth}}$	0.75	-	Efficiency of converting metabolites from reserves to soma	-
$k_{\text{conversion\_reserves}}$	0.85	-	Efficiency of converting metabolites between blood and reserves	-
k_{foraging}	0.2	-	Scaling factor for energetic cost of foraging	-
k_{growth}	0.28	-	Upper limit for proportional increase in structural body mass	-
$k_{\text{Fultons\_max}}$	$1.2{\cdot}10^{-8}$	0.01 g cm^{-3}	Fulton's condition factor for fish with full reserves	(Lambert and Dutil, 1997b)
$k_{\text{Fultons\_min}}$	$0.85{\cdot}10^{-8}$	0.01 g cm^{-3}	Fulton's condition factor for lean fish	(Lambert and Dutil, 1997b)
$k_{\text{MinutesPerWeek}}$	10080	-	Number of minutes in one time step	-
k_{OXF}	5	-	Scaling factor for effect of OXF on intake (including urinary and fecal energy loss)	-
k_{scope}	$2.58{\cdot}10^{-5}$	J min^{-1} g^{-b}	Coefficient for calculation of maximum aerobic scope	(Claireaux et al., 2000)
k_{SDA}	0.15	-	Coefficient for calculation of SDA	-
k_{SMR}	89596.7	J min^{-1} g^{-a}	Scaling factor for standard metabolic rate	(Clarke and Johnston, 1999)
$k_{\text{THF\_scope}}$	0.24	-	Scaling factor determining the strength of THF on AMR	-
$k_{\text{THF\_SMR}}$	0.23	-	Scaling factor determining the strength of THF on SMR	-
m_{fixed}	0.01	$year^{-1}$	Background mortality rate (constant)	-
m_{foraging}	0.08	-	Coefficient for calculation of foraging-related mortality rate	-

$m_{\text{foraging}\times\text{scope}}$	0.9	year	Coefficient for calculation of active-while-vulnerable mortality rate	-
m_{scope}	0.8	-	Coefficient for calculation of scope-related mortality rate	-
m_{size}	0.038	year^{-1} cm$^{-x_{\text{size}}}$	Coefficient for calculation of size-dependent mortality rate	-
x_{foraging}	2	-	Exponent for calculation of foraging-related mortality rate	-
x_{scope}	3	-	Exponent for calculation of scope-related mortality rate	-
x_{size}	-0.75	-	Exponent for calculation of size-dependent mortality rate	-
α_{max}	1500	pg ml^{-1}	Maximum value of OXF	-
γ_{max}	200	ng ml^{-1}	Maximum value of GHF	-
τ_{max}	5	ng ml^{-1}	Maximum value of THF	-

Table S2. Variables used in a state-dependent fish growth model using optimized hormonal strategies.

Variables		
Name	**Unit**	**Definition**
$A_{\max}$	J min^{-1}	Maximum aerobic scope under influence of THF
A_{standard}	J min^{-1}	Maximum aerobic scope (AMR)
B_{foraging}	-	Foraging behaviour
C	J min^{-1}	Energetic costs of building new tissue (soma and reserves)
C_{growth}	J	Energy incorporated in new structural tissue
E	-	Food abundance in environment
I	J min^{-1}	Intake (corresponds to metabolizable energy)
L	cm	Body length
M	year^{-1}	Total mortality rate
M_{foraging}	year^{-1}	Foraging-related mortality rate
$M_{\text{foraging}\times\text{scope}}$	year^{-1}	Active-while-vulnerable mortality rate
M_{scope}	year^{-1}	Scope-related mortality rate
M_{size}	year^{-1}	Size-dependent mortality rate
P	J min^{-1}	Metabolic processes
P_{foraging}	J min^{-1}	Swimming cost of foraging behaviour
P_{growth}	J min^{-1}	Cost of converting metabolites from reserves into new structural tissue
P_{reserves}	J min^{-1}	Cost of converting metabolites from bloodstream into fat and proteins for storage
P_{SDA}	J min^{-1}	Cost of digestion and energy uptake into bloodstream
P_{SMR}	J min^{-1}	Standard metabolic rate (SMR) under influence of THF
P_{standard}	J min^{-1}	Standard metabolic rate (SMR)
$P_{\text{structure}}$	J min^{-1}	Standard metabolic rate based on structural weight
R	J	Energy reserves
$R_{\max}$	J	Maximum reserves depending on body size
ΔR	J	Energy incorporated in reserves (when negative, reserves are drained)
S	year^{-1}	Survival probability
W	g	Body mass (structural and reserves)
$W_{\text{structure}}$	g	Structural body mass
$\Delta W_{\text{structure}}$	g week^{-1}	Growth
α	pg ml^{-1}	Level of OXF
γ	ng ml^{-1}	Level of GHF
τ	ng ml^{-1}	Level of THF

Table S3

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Table S4

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