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Structural peculiarities in the FOXO1 signaling pathway mediated differences in the dynamics of neuropeptides expression regulating feeding behavior in slow- and fast-growing chickens

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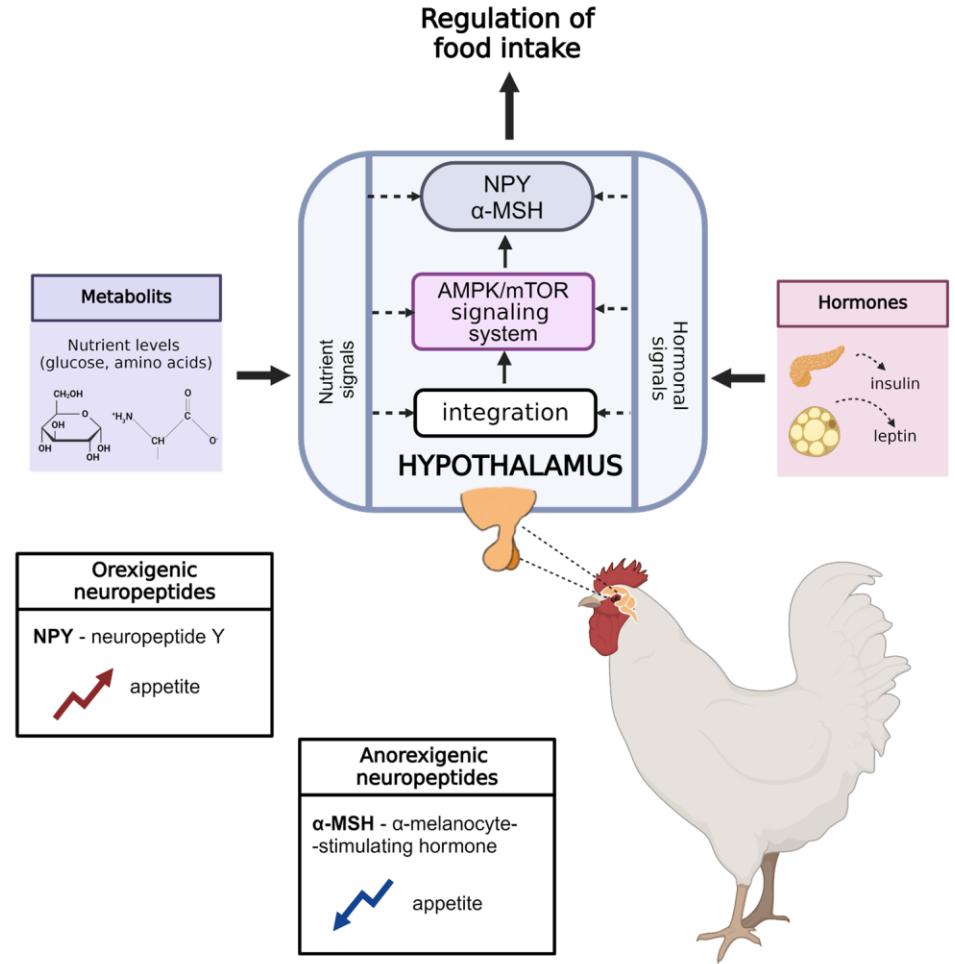
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Research objective

Chickens feeding behavior is regulated in the hypothalamus by altering the expression of specific neuropeptides: **orexigenic NPY** (appetite-stimulating) and **anorexigenic α -MSH** (appetite-suppressing), derived from **POMC** precursor. This regulation is closely related to the signaling of hormones **leptin** and **insulin**, which influence neuropeptide expression through the **AMPK/mTOR** signaling pathway.

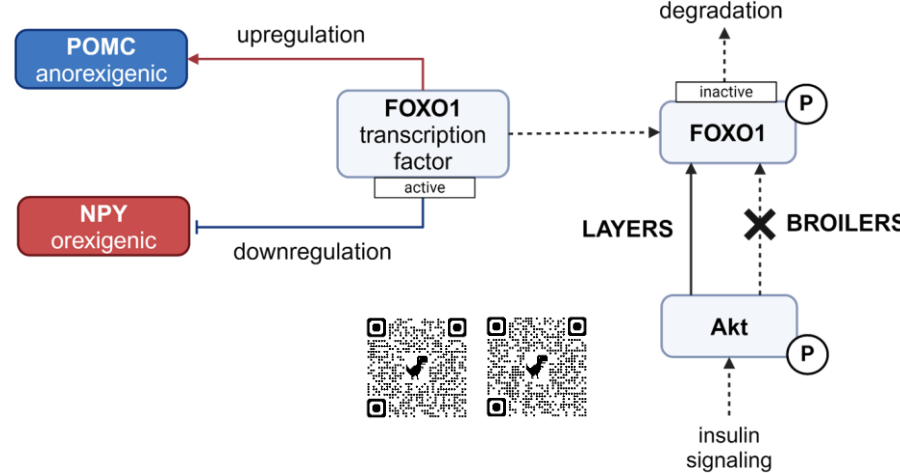
Multiple interactions between signaling pathways involved in the regulation of feeding behavior result in complex dynamic behavior of this system that is not intuitively predictable.

Thus, the application of a **mathematical modeling approach**, including the development of detailed mechanistic and modular models, is critical to further study the molecular mechanisms and their influence on feeding behaviour and energy balance in chickens.



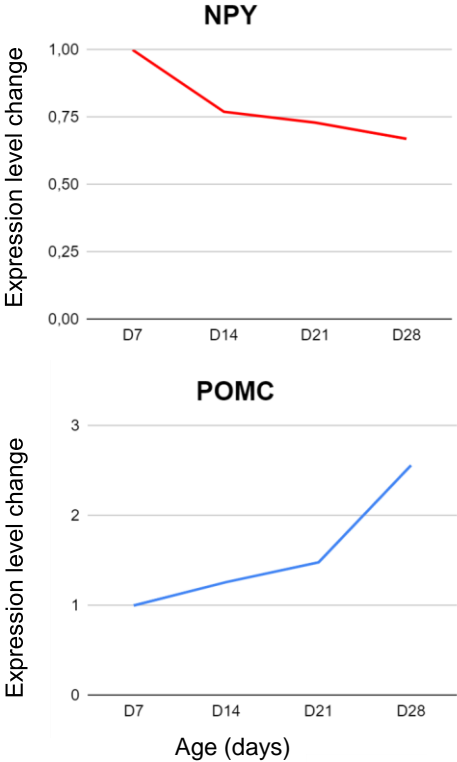
Motivation

Selecting chickens with high growth rates has led to the inability of broilers to adequately consume feed commensurate with energy needs. In meat breeds of chickens, unlike layers, expression of the **appetite-suppressing gene *POMC* decreases with age** (Saneyasu *et al.*, 2013), potentially contributing to overeating. This observation might be linked to **variations in signaling of the transcription factor FOXO1**, which activates *POMC* gene expression (Saneyasu *et al.*, 2018, 2019).



Experimental data

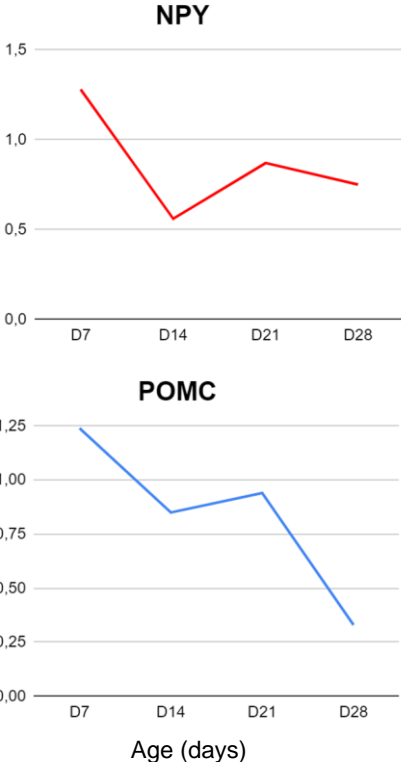
LAYERS



Honda *et al.*, 2015



BROILERS



Saneyasu *et al.*, 2013



Methods

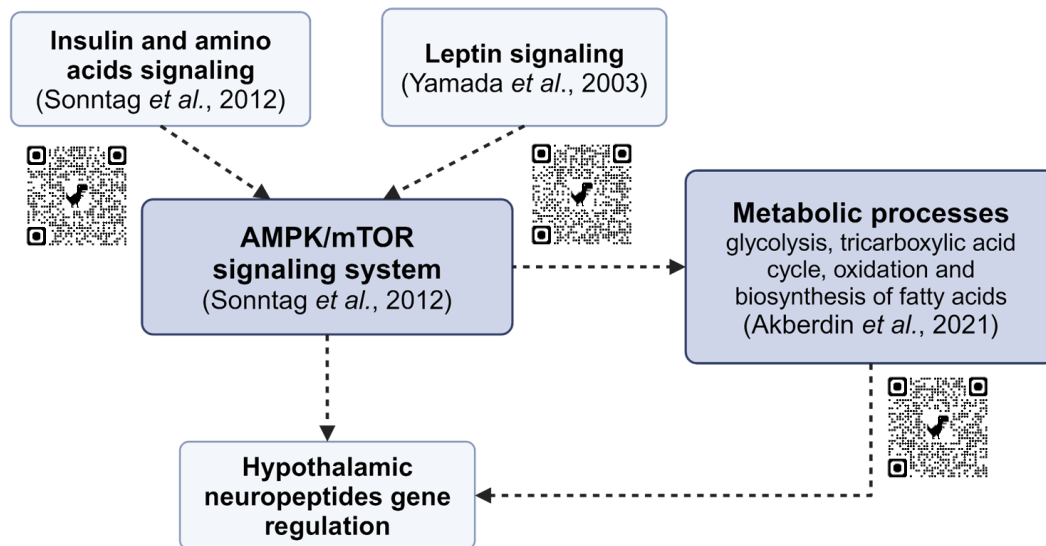
Mathematical models: describing the mechanisms of food intake regulation in broiler and layer chicken hypothalamic cells were reconstructed in the open access **BioUML software package** (Kolpakov *et al.*, 2022).



The structure of the developed model is based on following models:

1. **AMPK/mTOR** signaling system regulated by **amino acid** and **insulin** signaling (Sonntag *et al.*, 2012);
2. **Leptin** signaling pathway (Yamada *et al.*, 2003);
3. The cytosolic, mitochondrial and transport modules describing **metabolic processes** in human skeletal muscles (Akberdin *et al.*, 2021).

To expand models nucleus module describing the **expression regulation of hypothalamic neuropeptides** (NPY, AgRP and POMC) was created.

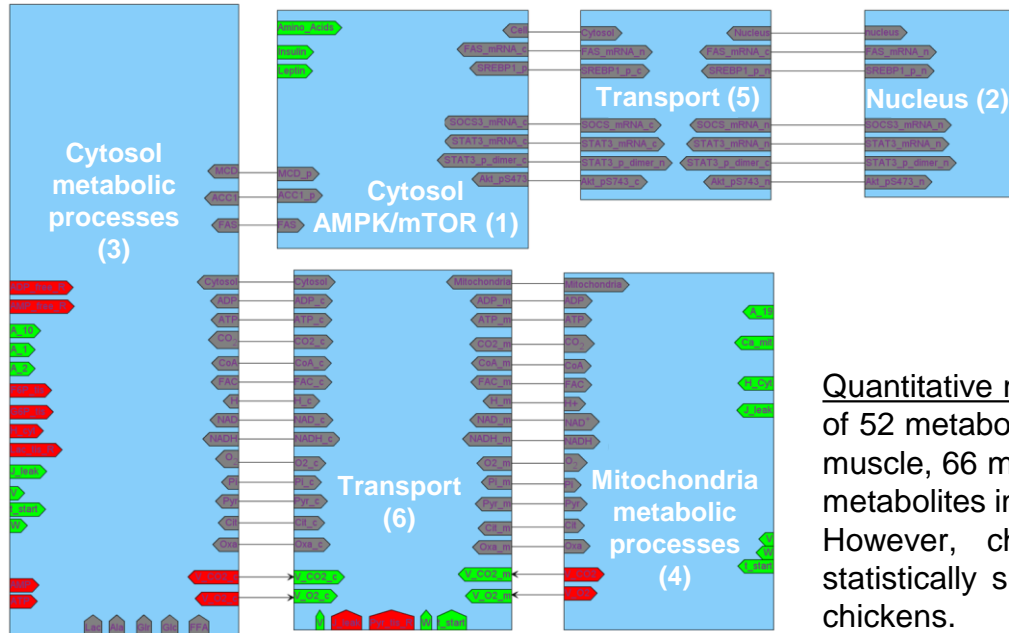


Quantitative metabolomic analysis of chicken tissues: was carried out using the NMR method. Metabolomic extracts of chicken **heart, liver, kidney, breast and leg** muscle from 12 samples were taken from **slow growing chickens** and 12 samples from **fast growing chickens**. Quantification of NMR data was performed by integrating the NMR signals relative to an internal standard.

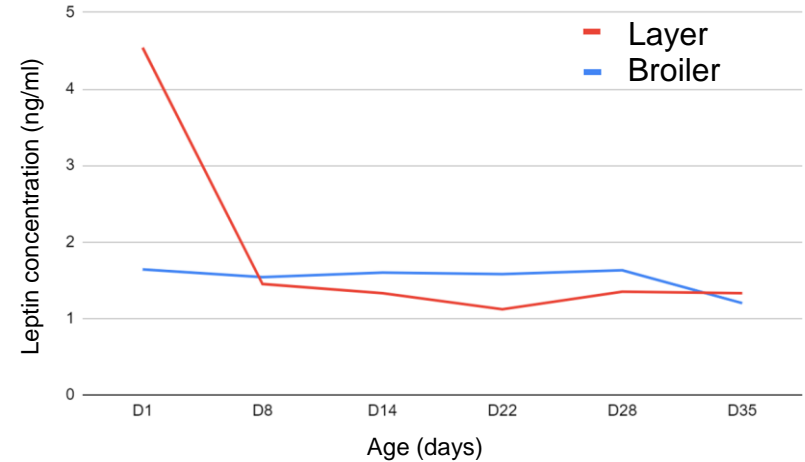
Results

Mathematical models: Two composite mathematical models were built, consisting of **6 modules**:

1. Cytosol: the AMPK/mTOR signaling pathway regulated by insulin, leptin and amino acids signaling;
2. Nucleus: the regulation of neuropeptides expression;
- 3-4. Cytosol and mitochondria: metabolic processes considering changes in the concentration of measured metabolites;
- 5-6. Transport modules.



As part of the modeling of **free-feeding conditions** for slow and high growth rate chickens, based on experimental data, approximating functions were proposed that describe **changes in leptin concentration** in layer and broilers depending on the age (Cassy *et al.*, 2004).



Quantitative metabolomic analysis of chicken tissues: the concentrations of 52 metabolites in the chicken breast muscle, 57 metabolites in the leg muscle, 66 metabolites in the heart, 75 metabolites in the kidney, and 74 metabolites in the liver.

However, chemometric analysis did not reveal metabolites with statistically significant differences between slow- and high growth rate chickens.

Results

Mathematical models: Models have been fitted to **hypothalamic neuropeptides NPY and POMC** mRNA levels in broiler and layer chickens (Honda *et al.*, 2015; Saneyasu *et al.*, 2013).

The structural differences in the regulation of the expression of these genes were based on the experimentally identified difference between two breeds of chickens:

In broilers, FOXO1 was not phosphorylated in the insulin signaling pathway.

Conclusion

1. The mechanism of FOXO1 transcriptional regulation made it possible to obtain differences in the dynamics of expression of the *POMC* and *NPY* genes in accordance with experimental data. These differences might explain the difference in feeding behavior between broilers and layers.

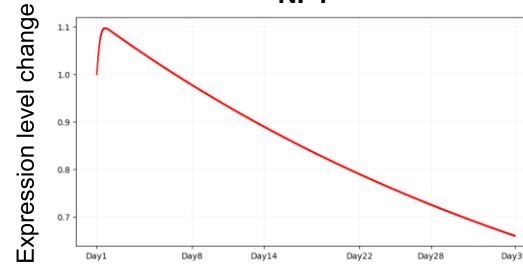
2. It is possible that the metabolomic differences are too small compared to the variation within each group, and a significantly larger sample size must be used to detect these differences.

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Models' predictions

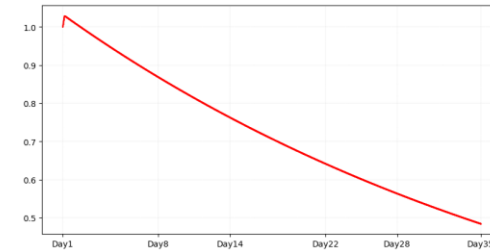
LAYERS

NPY

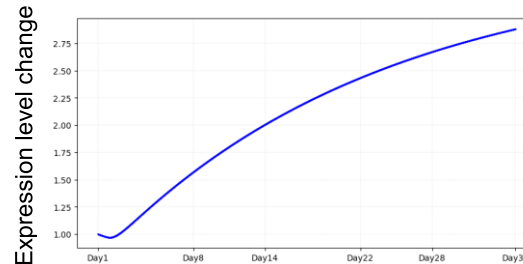


BROILERS

NPY



POMC



POMC

