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A dynamic model to simulate potassium balance in dairy cows.

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A dynamic Model to simulate Potassium Balance in Dairy Cows.

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ABSTRACT

High performing dairy cows require a particular composition of nutritional ingredients, adapted to their individual requirements and depending on their production status. The optimal dimensioning of minerals in the diet, one of them being potassium, is indispensable for the prevention of imbalances. The potassium balance in cows is the result of potassium intake, distribution in the organism, and excretion, it is closely related with the glucose and electrolyte metabolism. In this paper, we present a dynamical model for the potassium balance in lactating and non-lactating dairy cows based on ordinary differential equations. Parameter values are obtained from clinical trial data and from the literature. To verify the consistency of the model, we present simulation outcomes for three different scenarios: potassium balance in (i) non-lactating cows with varying feed intake, (ii) non-lactating cows with varying potassium fraction in the diet, and (iii) lactating cows with varying milk production levels. The results give insights into the short and long term potassium metabolism, providing an important step towards the understanding of the potassium network, the design of prophylactic feed additives, and possible treatment strategies.

Key words. dairy cow, potassium balance, mathematical model, ordinary differential equation, network

INTRODUCTION

Potassium is quantitatively the third most present monovalent cation in the body. It is fundamental for cell functioning, being involved in regulation of osmotic pressure, signal transduction, acid-base regulation, nerve impulse transmission and muscle contraction. Potassium needs to be taken up continuously with the diet (National Research Council, 2001). After absorption from the intestinal tract, potassium is distributed dynamically between intra- and extracellular space in all tissues. Its main excretion pathway is via urine through the kidneys. However, our knowledge about detailed mechanisms and regulation of potassium balance in mammals is still incomplete (Youn and McDonough, 2009).

High performing dairy cows require a particular composition of nutritional ingredients depending on their production status. The optimal dimensioning of minerals in the diet including potassium is indispensable for the prevention of imbalances. Current nutritional recommendations propose a low potassium diet before calving (Goff, 2006). In cattle and other mammals the serum potassium concentration is maintained in the narrow range between 3.5 and 5.8 mmol/L (Sejersted and Sjøgaard, 2000). But, with an intracellular potassium concentration between 7 and 70 mmol/L in erythrocytes (Christinaz and Schatzmann, 1972), minor damages of cells can lead to a large overestimation of serum potassium content (Sejersted and Sjøgaard, 2000). In recent years, measurement methods have been improved, and hypokalemia has increasingly been diagnosed in cows linked with metabolic and mineral imbalances, abomasal displacement, ketosis and recumbency (Sattler et al., 1998; Peek et al., 2000; MokhberDezfouli et al., 2013). This motivates our research on this topic.

Potassium balance closely interacts with glucose and electrolyte metabolism (Grünberg et al., 2006). That is, elevated glucose blood levels lead to a rise in blood insulin, which favors the potassium shift to the intracellular space. Postpartum veterinary treatments frequently intervene in glucose metabolism by administration of dextrose infusion and corticosteroids administration. Both have been shown to favor hypokalemia (Sattler et al., 1998; Peek et al., 2000; Grünberg et al., 2006). Sodium, Potassium and chloride are important players in the maintenance of osmotic pressure and acid base homeostasis. Changes in their concentration affect potassium homeostasis, that is, acidosis leading to potassium shift from intra-cellular fluid (ICF) to extra-cellular fluid (ECF) and alkalosis vice versa (Adrogué 1981). Clinical relevance and application is reviewed in Russell et al. 2007 and Biff et al. 2016.

Studying veterinary and mathematical aspects, we have developed a quantitative, dynamic model for potassium balance in dairy cows. We focus on the whole organism instead of cellular level, with an emphasis on metabolic flows between components (e.g. gastrointestinal tract, milk). We compare

the outcome of the model simulations with experimental data in a qualitative manner, since the interindividual variability is too large to reproduce the data exactly.

To our knowledge, there is no published work that presents a bio-mathematical model of the potassium balance in dairy cows, or in another livestock species, yet. Mathematical modeling of the involved mechanisms generates quantitative knowledge of the underlying biological processes enabling predictions about the intake and outputs, the distribution of potassium within the body.

A preliminary model was published in a technical report (Plöntzke et al. 2013).

The long-term goal behind developing such a model is to gain more insight into the mechanistic background, to assist the development of feed additives and effective treatment strategies. The model will be open access available in Systems Biology Markup Language (SBML) format on BioModels Database¹. It can be used by the scientific community and industry to support ration calculation, herd- and individual cow management.

MODEL DEVELOPMENT

The modeling objective was to obtain a system of ordinary differential equations (ODEs) and algebraic equations, which is able to simulate the dynamics of potassium balance in dairy cows. Practical mathematical tools for modeling stimulatory or inhibitory effects are positive and negative Hill functions:

$$H^+(S, T; n) = \frac{(S/T)^n}{1+(S/T)^n}, H^-(S, T; n) = \frac{1}{1+(S/T)^n}$$

Here, $S \geq 0$ denotes the influencing substance, $T \geq 0$ the threshold, and $n \geq 1$ the Hill coefficient.

A Hill function is a sigmoidal function between zero and one that switches at the threshold $S = T$ from one level to the other with a slope specified by n and T .

To build up essential components for potassium balance, the model was designed on a whole organism level, based on clinical study data and scientific knowledge. The model consists of 12 ODEs, 4 algebraic equations and 63 parameters. All simulations were conducted in the software CellDesigner (Ver. 4.4) using the solver SOSlib. The mechanisms of the model are pictured in the flowchart in figure 1. Model components and their units are summarized in table 1. Table 2 contains the list of parameter values and units.

¹ www.ebi.ac.uk/biomodels-main/

Experimental Data

In the Clinic for Ruminants of Freie Universität Berlin a clinical study was conducted to study potassium balance in six non lactating dairy cows. Experimental data from this study were available for parameter estimation, which was performed with the algorithms NLSCON (Deuflhard, 2004) and simulated annealing (Kirkpatrick, 1983). In the dataset from the clinical study, we noticed strong inter-individual variations between the six study cows, most notably in intracellular potassium and insulin measurements. In the preliminary model of potassium balance in Plöntzke et al. (2013) we set some parameters to cow-specific values. Thus, we obtained specific parameter sets that adapt the model behavior to the considered cow. The default condition of the herein presented advanced model is based on this dataset in a quantitative way, as well as on values from literature. Finally, we obtained a deterministic model that reproduces the potassium balance of an average cow.

Units

To obtain a model for potassium balance with uptake and excretion and to account for distribution inside the organism, the model needs to handle masses and concentrations and to convert between those. The in- and output components K_{FEED} (potassium uptaken with diet, Tab 1) and K_{URIN} (potassium excreted with urine, Tab 1) are specified in gram per hour and gram (accumulated), respectively. The amount of potassium taken up from K_{FEED} is dissolved in the non-cellular compartment of the cow's blood, K_{ECF} (potassium in the extracellular blood fluid, Tab 1).

For the conversion of mass to concentration we need the volume in which the substances are dissolved. Blood volume calculation is made on the base of 55 ml blood per kg bodyweight as reported by Reynolds (1953). The bodyweight is set to 600 kg in the default condition. The intra- and extracellular volume of blood tissue are calculated with the mean hematocrit from the experimental data, which represents the volume of the cellular components in the blood.

The model contains two compartments: the extracellular and the intracellular fluid of the blood. The components K_{ECF} , $Gluc_B$ (Glucose in blood, Tab 1), and *Insulin* (Insulin in blood, Tab 1) are located in the extracellular compartment, which has the volume $V_{extra}= 22.8$ L. The intracellular compartment includes only the component K_{ICF} (potassium in the intracellular blood fluid, Tab 1) and has the volume $V_{intra}= 10.2$ L. The absolute blood volume of the modeled cow is therefore 33 L. The calculations that lead us to the volumes are explained with more details in Plöntzke et al. (2013).

Mechanisms

Potassium balance is determined by dietary potassium content, its absorption, homeostasis and excretion. Potassium homeostasis is characterized by fluent intra- and extracellular drift, powered by numerous passive and active forces, and regulated by complex interactions which are not completely understood, yet. The default condition of the present model is based on the experimental dataset described above as well as on literature as described in the following section. Concerning notation, rates are named $X_{source} X_{target}$, indicating source and target of a shift of substance X. State variable in the differential equations are denoted with y .

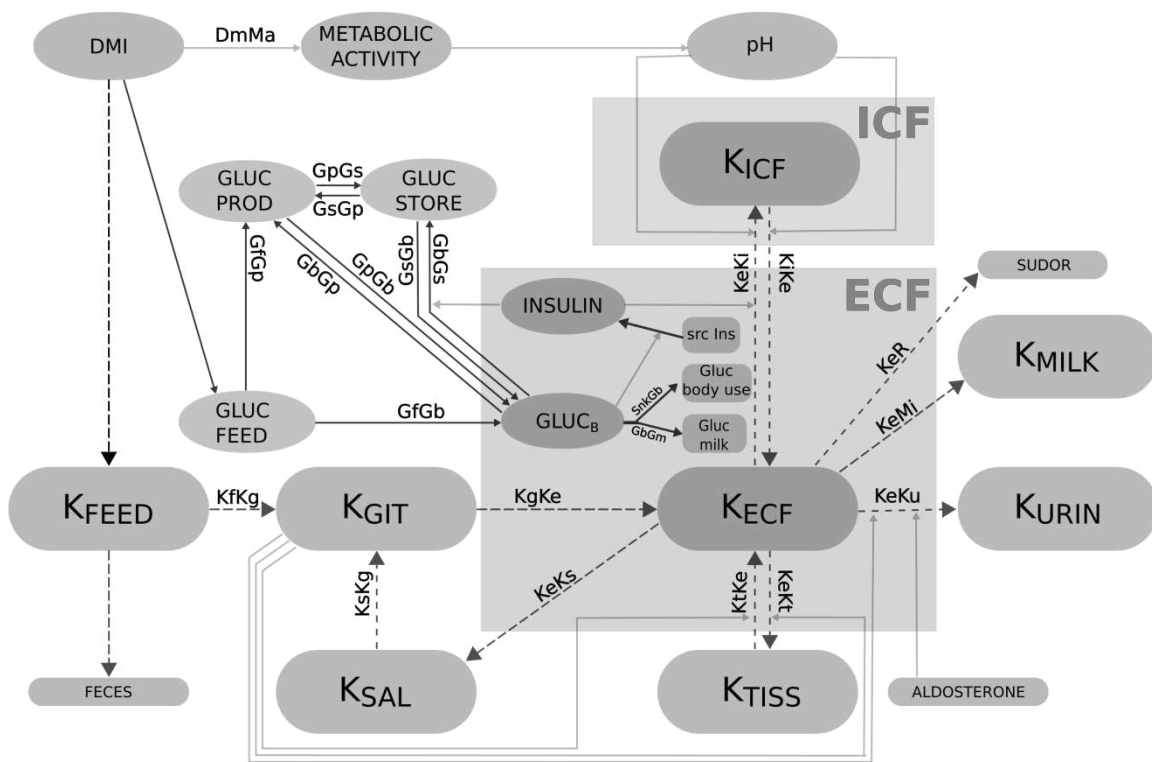


Figure 1: Schematic representation of the components and relationships in the herein presented model of potassium balance in the dairy cow. Each big box represents one model component as explained in Table 2. Dashed lines represent potassium flow rates and solid lines glucose flow rates. The light grey arrows represent stimulatory and inhibitory effects. Two light grey boxes in the background stand for the extracellular (ECF) and intracellular (ICF) blood compartment, with a volume of 22.8 L and 10.2 L, respectively.

Potassium Uptake

Feed intake. The model cow ingests a certain amount of food, which is modeled by an algebraic equation for *DMI* (dry matter intake) in gram per hour. *DMI* is input and driving force of the model. It can be varied by changing parameter p_{54} , as a percentage of the default condition, i.e. $p_{54}=1$ means 100 % of the amount in the default condition. We assume that the cow is not eating continuously over daytime, so a periodic function with a period length of 24 h was chosen to describe feed ingestion.

$$\mathbf{DMI}: y_{DMI} = p_{54} \cdot 487.5 \cdot \left(1 - \sin\left(\frac{\pi \cdot t}{12}\right)\right)$$

Integrating y_{DMI} over 24 h, we obtain a daily intake for *DMI* of $24 \cdot y_{DMI}(0)$. The study protocol provides an intake of 11700 g *DMI* per 24 h. With $y_{DMI}(0) = 487.5$ g per h in default condition, this value is exactly reached.

In the model, the ingested amount of potassium is represented by K_{FEED} . From the clinical study, potassium uptake was given with 133 g per day, which is set as default condition in the model.

To conduct simulations with different amounts of potassium, the potassium content of *DMI* can be varied by changing p_{56} , representing the percentage of potassium in *DMI*.

$$\mathbf{K}_{FEED}: y_{K_{FEED}} = p_{56} \cdot y_{DMI}$$

Potassium Absorption. Mechanisms of potassium absorption differ in details among the different segments of the gastrointestinal tract (GIT). Hence, we pool this whole system in one component K_{GIT} .

The absorption of potassium from diet is up to 97 % in the cow and increases with increasing amounts of potassium in the rumen (Reynolds et al., 1991). In the model, 95 % ($p_{30}=0.95$) of K_{FEED} is passing continuously to the gastrointestinal tract K_{GIT} with the rate $KfKg$.

$$KfKg = p_{30} \cdot y_{K_{FEED}}$$

In K_{GIT} , potassium accumulates and is absorbed to K_{ECF} with the rate $KgKe$.

$$KgKe = p_{31} \cdot y_{K_{GIT}}$$

Besides K_{FEED} , potassium additionally arrives at K_{GIT} with saliva at the rate $KsKg$.

$$KsKg = p_{32} \cdot y_{K_{SAL}}$$

$$K_{GIT}: \frac{d}{dt} y_{K_{GIT}} = KfKg - KgKe + KsKg$$

Metabolic Components

Potassium balance closely interacts with other metabolic networks. To keep the system in reasonable dimensions, we model a minimal number of metabolic components. The current model contains excerpts from glucose and acid-base metabolism.

Glucose Metabolism. Glucose metabolism and homeostasis are of special concern in any mammal, because glucose is an essential substrate for tissues, e.g. the nervous system and the erythrocytes, amongst others (Stangassinger, 2005). For the model, the glucose-insulin metabolism is of special interest due to its interaction with the cellular uptake of potassium. Furthermore, there are common pharmaceutical interventions in the glucose metabolism, as application of glucocorticoids, whose effects on potassium balance have not been studied, yet.

Glucose metabolism in ruminants is different compared to monogastric species, due to the fermentative character of their digestion. Dietary carbohydrate resorption as hexose sugar is very low in the ruminant. Carbohydrates ingested with the *DMI* are digested by microbes under anaerobic conditions via glycolysis and pentose phosphate cycle to the intermediary product pyruvate and in the following to the short chain fatty acids acetate, propionate and butyrate (Breves and Leonhard-Marek, 2005). These short chain fatty acids are then resorbed and serve, amongst others, as precursor substances for gluconeogenesis.

When *DMI* contains high amounts of starch that cannot be metabolized in the rumen, so called bypass starch, this fraction can be split enzymatically in the small intestine and then be resorbed as glucose.

The fraction of glucogenic substances and resorbable glucose from *DMI* is pooled in the component *GlucFEED*. *GlucFEED* is modeled with an algebraic equation and set to 8.5 % of *DMI* in the default condition. It can be varied according to the diet via p_{46} .

$$Gluc_{FEED}: y_{Gluc_{FEED}} = p_{46} \cdot y_{DMI}$$

Up to 90% of the glucose need in the cow has to be covered by gluconeogenesis (Brockman, 1993). Glucose need depends on individual demand, determined by production, lactational status,

pregnancy, diet composition, and other factors. After resorption of glucose precursor substances, gluconeogenesis is enhanced in the organism and blood glucose levels rise.

With the rate $GfGp$ glucogenic substances are transported to the component $GlucPROD$. In this component, we pool the endogenous production of glucose in the organism.

$$GfGp = (1 - p_{48}) \cdot y_{GlucFEED}$$

The remaining part of $GlucFEED$ goes to the component $GlucB$, representing blood glucose, with the rate $GfGb$. This rate represents direct glucose absorption from the intestine, including bypass starch.

$$GfGb = p_{48} \cdot y_{GlucFEED}$$

Glucose is taken out of the storage for gluconeogenesis to the $GlucPROD$ component with the rate $GsGp$. This rate is reduced in the case of high $GlucFEED$ levels, modeled with a Hill function, to guarantee the pathway of $GfGp$ to be preferred when high amounts of glucogenic substances in feed are available. If $GlucSTOR$ becomes low, a Hill function deactivates the rate.

$$GsGp = p_{60} \cdot H^-(y_{GlucFEED}, p_{61}, 5) \cdot H^+(y_{GlucSTOR}, p_{35}, 10)$$

Glucose produced in $GlucPROD$ is transported to $GlucB$ with the rate $GpGb$, except in the case of too high blood glucose levels, when a Hill function switches off the rate.

$$GpGb = p_{39} \cdot y_{GlucPROD} \cdot H^-(y_{GlucB}, p_{50}, 10)$$

The excess of produced glucose is going back to $GlucSTOR$ with the rate $GpGs$, which is switched off when the storage is full. If the modeled cow is producing more than 24 L milk per day ($p_{55} > 1$ L/h), the rate is also switched off to make the maximal amount of glucose available for milk production and to reduce the contrary pathways.

$$GpGs = p_{51} \cdot y_{GlucPROD} \cdot H^-(y_{GlucSTOR}, p_{57}, 10) \cdot H^-(p_{55}, p_{62}, 10)$$

$$GlucPROD: \frac{d}{dt} y_{GlucPROD} = GfGp - GpGb - GpGs + GsGp$$

In vivo, glucose is stored as glycogen. The component $Gluc_{STOR}$ represents the pooled glucose storage of an individual. We consider muscle, liver and kidney as the main tissues storing glucose, and calculate the mass of them with around 280 kg, whereof 9 kg is liver weight (Pfuhl et al., 2005), for a cow with 600 kg bodyweight as in the default condition. Glycogen content in muscle was reported with 45 to 108 mmol/kg in cattle, with a mean of 78 mmol/kg (Immonen et al., 2000). We assume that there is a maximum storage capacity, which cannot be exceeded, not even with increasing carbohydrate uptake. We calculate the dimension of this storage with 2% glycogen weight in the muscle tissue and 10% in liver (Berg et al., 2002). So, in 9 kg liver there can be stored 900 g glycogen, and about 5300 g can be stored in muscle with a weight of 265 kg. Finally, we obtain a maximum storage capacity of 6200 g.

Glucose is transported from the storage to the blood with the rate $GsGb$. The rate increases for low levels of $Gluc_B$ and diminishes for high levels of $Gluc_B$, which is implemented using the term $p_7 - y_{Gluc_B}$. The second part of the rate is only active if milk production is higher than about 5 L per day ($p_{55} > 0.2$ L/h) and is enhancing the rate to provide $Gluc_B$ with enough glucose for the milk.

$$GsGb = H^+(y_{Gluc_{STOR}}, p_{35}, 10) \cdot H^-(y_{Gluc_{FEED}}, p_1, 10) \cdot p_{17} \cdot (p_7 - y_{Gluc_B}) + H^+(p_{55}, p_{64}, 10) \cdot p_{63} \cdot H^-(y_{Gluc_B}, p_{65}, 10)$$

Insulin promotes the transport of glucose from $Gluc_B$ to $Gluc_{STOR}$ with the rate $GbGs$. Similarly, as for $GpGs$, milk production, controlled by parameter p_{55} , causes a reduction of the rate, implemented via a Hill function, since glucose is needed then for the milk and is not stored. For low levels of $Gluc_{FEED}$ and for the case of an already full $Gluc_{STOR}$, the rate also decreases, modeled via Hill functions.

$$GbGs = H^+(y_{Gluc_{FEED}}, p_1, 10) \cdot p_{12} \cdot y_{Gluc_{PROD}} \cdot H^-(y_{Gluc_{STOR}}, p_{57}, 10) \cdot y_{Gluc_B} \cdot y_{INS} \cdot H^-(p_{55}, p_{36}, 10)$$

$$Gluc_{STOR}: \frac{d}{dt} y_{Gluc_{STOR}} = GbGs - GsGb + GpGs - GsGp$$

The clearance rate of blood glucose, $SnkGb$, representing the metabolic use, depends on the current levels of $Gluc_B$ and $Gluc_{PROD}$. It contains an extra term for the glucose needed for milk production, p_{55} (the milk production in L/h) multiplied by $p_{47}=72$ g/L, representing the amount of glucose that is

needed to produce one liter of milk, see Kronfeld (1982). A Hill function fades out the rate for extreme low levels of $Gluc_B$. When the model cow is producing milk, i.e. $p_{55} > 0$ L/h, the dependency on $Gluc_{PROD}$ is reduced by the term $e^{-p_{66} \cdot p_{55}}$. It has the value 1, and therefore no influence, when parameter p_{55} is 0 L/h. This modeling approach accounts for the fact that, in the case of high milk production and high feed intake, the high excess of produced glucose is available for milk and not for metabolic use of non-mammary tissues (Reynolds, 2005).

$$SnkGb = H^+(y_{Gluc_B}, p_{58}, 10) \cdot (p_{28} \cdot y_{Gluc_B} + p_{59} \cdot y_{Gluc_{PROD}} \cdot e^{-p_{66} \cdot p_{55}} + p_{55} \cdot p_{47})$$

$$\mathbf{Gluc_B}: \frac{d}{dt}(y_{Gluc_B} \cdot V_{extra}) = GfGb - GbGs + GsGb - SnkGb + GpGb$$

Glucose and Insulin dynamics influence each other. *Insulin* in the blood increases in response to rising levels of $Gluc_B$. In vivo, insulin is secreted from pancreatic beta cells in response to elevated blood levels of nutrients such as glucose or amino acids (Schuit, 2001).

In vivo, insulin is secreted from pancreatic beta cells in response to elevated nutrients such as glucose or amino acids. Glucose sensor cells have been found in pancreas, hypothalamus, and gut (Schuit, 2001).

It causes glucose uptake into cells of liver, muscle, and storage as glycogen inside these tissues. Furthermore, it causes cellular uptake of potassium in insulin sensitive cells by enhancing the activity of Na/K-ATPase (Youn and McDonough, 2009).

$$\mathbf{Insulin}: \frac{d}{dt}(y_{INS} \cdot V_{extra}) = p_{49} \cdot y_{Gluc_B} - p_{41} \cdot y_{INS}$$

Acid-base Metabolism. We introduced the dimensionless, artificial component *Metabolic activity* that enables us to model the relationship between acid base metabolism and the amount of feed intake. *DMI* stimulates *Metabolic activity* with the rate $DmMa$, which has a base value and declines when *DMI* is under a certain threshold. The sink term $p_{44} \cdot y_{MA}$ guarantees that *Metabolic activity* represents the recent feed intake and does not accumulate.

$$DmMa = p_{45} + p_{42} \cdot H^+(y_{DMI}, p_{43}, 2)$$

$$\mathbf{Metabolic Activity}: \frac{d}{dt}y_{MA} = DmMa - p_{44} \cdot y_{MA}$$

The pH has a base value, from which we subtract $1/40$ of *Metabolic activity* to obtain a decaying pH when *Metabolic activity* is high and vice versa.

$$pH: y_{pH} = 7.5 - \frac{y_{MA}}{40}$$

Potassium Homeostasis

Potassium homeostasis in the cow is characterized by a consistent flow of potassium cations between different compartments and tissues, in the model represented by the components K_{ICF} , K_{ECF} , K_{TISS} and K_{SAL} .

In the normokalemic cow, serum potassium concentration K_{ECF} is maintained between 3.5 to 5.8 mmol/L (Sejersted and Sjøgaard, 2000). High serum potassium levels (hyperkalemia) lead to heart arrhythmia and other severe dysfunctions in excitable cells (Unwin et al., 2011). Low serum potassium levels (hypokalemia) lead to a lack of motility and excitability of cells (Türck and Leonhard-Marek, 2010). In the model, after passing from K_{GIT} to K_{ECF} , potassium is moved to the intracellular fluid K_{ICF} , excreted with urine K_{URIN} and sudor, stored in tissue K_{TISS} or recycled via the saliva K_{SAL} to K_{GIT} .

Saliva. The component K_{SAL} represents the amount of potassium in saliva. Potassium in K_{SAL} is nourished by K_{ECF} with the rate $KeKs$.

$$KeKs = p_{18} \cdot y_{ECF} \cdot y_{DMI}$$

Depending on diet, cows produce up to 138-179 l saliva per day (Van'tKlooster et al., 1969) with an individually varying content of potassium between 0.16 to 2.94 g/l (Ward, 1966; Bailey, 1961).

Saliva is swallowed with the feed to the rumen, in the model from K_{SAL} to K_{GIT} with the rate $KsKg$ (see section Potassium Absorption).

$$K_{SAL}: \frac{d}{dt}y_{K_{SAL}} = KeKs - KsKg$$

Cellular Uptake. In the model, potassium is shifted from K_{ECF} to K_{ICF} with the rate $KeKi$, which is basically the constant parameter p_8 (Greenlee, 2009). Under certain conditions, $KeKi$ is modified as follows. If *Insulin* rises and passes the mean value p_3 from the study data, it enhances cellular uptake with the rate p_9 (DeFronzo et al., 1980). If pH is above the mean value p_{20} from experimental data, $KeKi$ is increased by p_{21} (Svendsen, 1969). If potassium in K_{ECF} drops under $p_{33}=2$ mmol/l the complete rate $KeKi$ is slowly switched off and becomes 0, to avoid a drop of K_{ECF} .

$$KeKi = (p_8 + p_9 \cdot H^+(y_{Ins}, p_3, 8)) \cdot H^+(y_{K_{ECF}}, p_{33}, 2) \cdot (1 + p_{21} \cdot H^+(y_{pH}, p_{20}, 10))$$

Cellular Exit. Potassium drifts from K_{ICF} to K_{ECF} with the rate $KiKe$.

Under certain conditions, the $KiKe$ rate is modified as follows. If pH drops under the threshold p_{20} , up to 100% more potassium drifts to K_{ECF} (Simmens and Avedon, 1959). If K_{ECF} drops under p_{29} , up to 100% more of potassium drifts from K_{ICF} to K_{ECF} (Greenlee, 2009). If K_{ICF} drops under p_{23} , the rate $KiKe$ gets slowly faded out to prevent K_{ICF} from getting too small. If K_{ICF} exceeds p_{14} , the rate is increased by p_{19} .

$$KiKe = (1 + H^-(y_{K_{ECF}}, p_{29}, 10)) \cdot p_5 \cdot (1 + H^-(y_{pH}, p_{20}, 10)) \cdot H^+(y_{K_{ICF}}, p_{23}, 2) \cdot (1 + p_{19} \cdot H^+(y_{K_{ICF}}, p_{14}, 2))$$

$$K_{ECF}: \frac{d}{dt}(y_{K_{ECF}} \cdot V_{extra}) = KgKe - KeKu - KeKt + KtKe + KiKe - KeR - KeKs - KeMi$$

$$K_{ICF}: \frac{d}{dt}(y_{K_{ICF}} \cdot V_{intra}) = KeKi - KiKe$$

Tissue Storage. K_{TISS} represents the potassium content in all tissues except blood and bone tissue.

The initial value of K_{TISS} depends on the bodyweight. Bennink et al. (1968) studied the potassium content of different tissues in cattle. They found mean potassium content of 3 g per kg bodyweight, which we used to calculate the initial value for K_{TISS} , representing the reservoir of potassium at the beginning of the simulation. K_{TISS} serves as a compensating potassium storage and fills up from K_{ECF} with the rate $KeKt$, which is only active when $K_{GIT} > p_{15}$.

We assume that the capacity of the tissue to store potassium is limited, which is implemented using a Hill function, that turns off $KeKt$ when K_{TISS} is full. The subtraction of p_{10} is used here to force the Hill function to switch faster, without using a very high Hill exponent that makes the equation numerically instable.

$$KeKt = H^+(y_{K_{GIT}}, p_{15}, 10) \cdot p_{25} \cdot y_{K_{ECF}} \cdot H^-(y_{K_{TISS}} - p_{10}, p_2 - p_{10}, 10)$$

Potassium leaves K_{TISS} to K_{ECF} with the rate $KtKe$ only when $K_{GIT} < p_{15}$.

$KtKe$ is intended to increase if K_{ECF} decreases, so the current rate $KtKe$ is a multiple of $p_{27} \cdot K_{ECF}$.

If K_{TISS} has diminished by 1% of its initial value p_{38} , then $KtKe$ is faded out with the help of a Hill function to account for the fact that only a part of potassium in the tissues can be mobilized into extracellular fluid.

$$KtKe = H^-(y_{K_{GIT}}, p_{15}, 10) \cdot p_{26} \cdot (p_{27} - y_{K_{ECF}}) \cdot H^+(y_{K_{TISS}} - p_{10}, 0.99 \cdot p_{38} - p_{10}, 10)$$

$$K_{TISS}: \frac{d}{dt} y_{K_{TISS}} = KeKt - KtKe$$

Potassium Excretion. Potassium is excreted mainly with urine (Ward, 1966), in the model K_{URIN} , with the rate $KeKu$. In addition, saliva and sudor contain remarkable amounts of potassium. Potassium content of saliva is represented by K_{SAL} . Potassium in sudor is fed by K_{ECF} with the rate KeR .

$$KeR = p_4 \cdot y_{K_{ECF}}$$

It is still not fully understood how serum potassium excretion is regulated exactly. There are known mechanisms and evidence based hypotheses. In hyperkalemia, urinary potassium excretion is regulated by aldosterone (Rabinowitz, 1996), a mineralocorticoid from the cortex of the adrenal gland. In the model, aldosterone action enhances excretion when K_{ECF} rises above p_{24} .

There is strong evidence for a feed-forward regulation of potassium excretion because an increase in excretion can be observed without significant rise in serum potassium (Lee et al., 2007). There are three supposed mechanisms for feed-forward regulation: (1) a gut receptor, which enhances potassium excretion after a potassium rich meal; (2) a portal vein receptor, which is confirmed to be bumetanide sensitive in the rat and (3) regulation from the central nervous system (Lee et al., 2007; Oh et al., 2011). The model accounts for feed-forward regulation via a direct dependency of $KeKu$ on the actual value of K_{GIT} .

Furthermore $KeKu$ rises if K_{ECF} grows above life-threatening levels, $K_{ECF} > p_{22} = 0.25 \text{ g/L}$, modeled again by a Hill function.

$$K_{URIN}: \frac{d}{dt} y_{K_{URIN}} = KeKu$$

$$KeKu = \left(1 + p_{13} \cdot H^+(y_{K_{ECF}}, p_{24}, 5)\right) \cdot p_6 \cdot y_{K_{GIT}} \cdot \left(1 + p_{16} \cdot H^+(y_{K_{ECF}}, p_{22}, 10)\right) + p_{53} \cdot y_{K_{ECF}}$$

Milk. In the model it is possible to switch on a constant milk production that can be varied individually via p_{55} representing milk production in L/h. Potassium content in milk is constant with $p_{52} = 1.4 \text{ g/L}$ (Pradhan and Hemken, 1968). However, Constable et al. (2013) showed that potassium

in milk can also vary. Potassium for milk is taken directly from K_{ECF} with the rate $KeKm$ that is turned off via a Hill function for very small levels of K_{ECF} to prevent it from becoming negative.

$$KeKm = p_{55} \cdot p_{52} \cdot H^+(y_{K_{ECF}}, p_{40}, 10)$$

$$K_{MILK}: \frac{d}{dt} y_{K_{MILK}} = KeKm$$

Glucose in milk is calculated considering a glucose demand for milk production of $p_{47}=72$ g per L milk (Kronfeld, 1982). If $Gluc_B$ is getting too low, the rate $GbMi$ is faded out via a Hill function.

$$GbMi = p_{55} \cdot p_{47} \cdot H^+(y_{gluc_B}, p_{58}, 10)$$

Since glucose in milk is not an actual component of the model, the rate $GbMi$ is part of the clearance rate of Glucose, $SnkGb$.

RESULTS AND DISCUSSION

Model mechanisms are validated with numerical experiments and clinical data. Within the experimental data, there is a large inter- and intra-individual variability. In particular, the values for K_{ICF} , the measured potassium content in erythrocytes, and insulin show a strong numerical variation. Thus we decided to evaluate simulation outcomes qualitatively. The simulation results represent a selection of possible numerical experiments. Simulation outcomes show the behavior of model components over time until the system converges to its steady state.

Note that potassium concentrations in literature are usually stated in mmol/L. The unit of K_{ECF} and K_{ICF} presented in the plots is mmol/L as well. For calculations the model uses g/L.

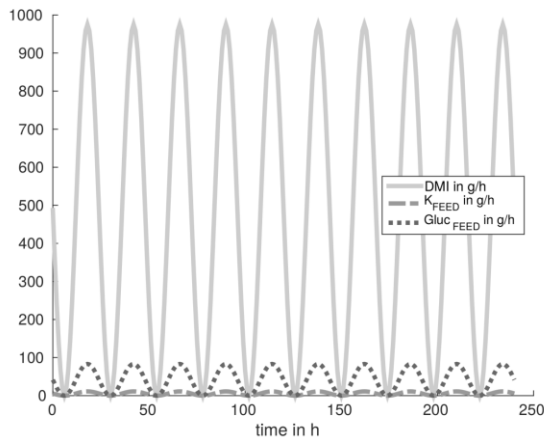
In the section **Default Condition**, we first present outcomes from the simulation of potassium balance without intervention in a non-lactating cow. To verify the consistency of the model, three experiments are performed: In experiment 1 the feed intake DMI is varied, in experiment 2, the potassium fraction in the diet K_{FEED} is varied and in experiment 3, simulation outcomes for a lactating cow are shown.

Default Condition

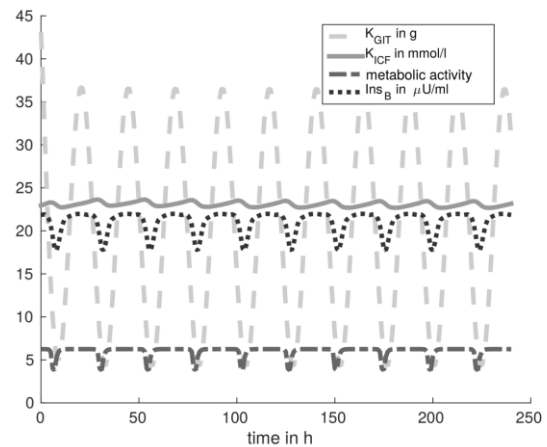
The default condition of this model is based on the experimental data that was used to build the preliminary model (Plöntzke et al., 2013, see Material and Methods). The study data were collected from 6 non lactating dairy cows. They were fed with 11.7 kg of DMI per day (fig. 2a) containing

1.137 % of potassium, which can be observed in the simulation of the component K_{FEED} (fig. 2a) leading to 133 g potassium uptake per day.

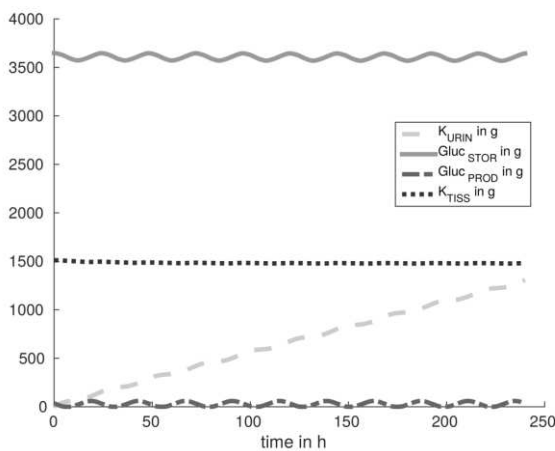
Figure 2: Simulation results for all model components in the default condition are shown, as described in the section Materials and Methods, simulated over 10 days. All model components show stable dynamics.



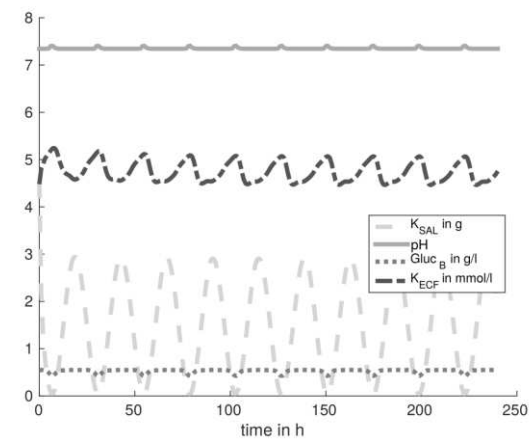
2a: K_{FEED} , $Gluc_{FEED}$, DMI



2b: K_{GIT} , K_{ICF} , $Metabolic\ activity$, $Insulin$



2c: K_{URIN} , K_{TISS} , $Gluc_{STOR}$ and $Gluc_{PROD}$

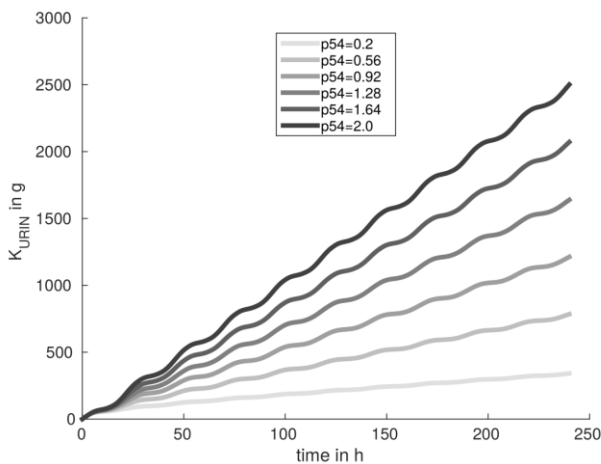


2d: K_{SAL} , K_{ECF} , $Gluc_B$, pH

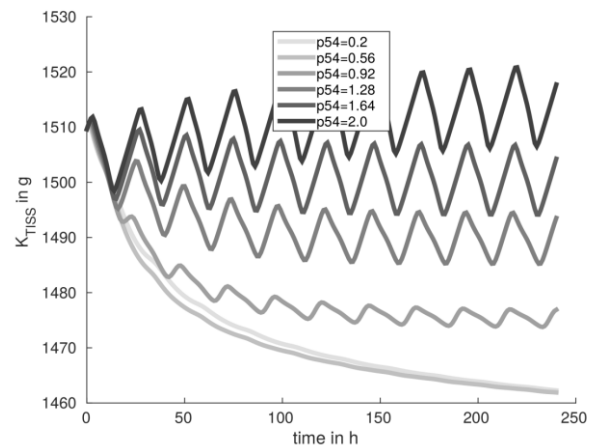
The component K_{GIT} (fig. 2b) pools the amount of potassium absorbed in the gastrointestinal tract. One can see here the potassium ingested with K_{FEED} , minus 5% which are obligatorily excreted with the feces, plus the potassium from saliva, K_{SAL} (fig. 2d), which is swallowed and absorbed to K_{GIT} . Potassium from K_{GIT} is passed to K_{ECF} , the extracellular fluid of the cow's blood. From there, potassium is moved to the intracellular fluid K_{ICF} (fig. 2b), excreted with urine K_{URIN} (fig. 2c) and sudor, or recycled via the saliva K_{SAL} to K_{GIT} . In the study of Bailey (1961), potassium content of saliva was measured between 0.156 g/L and 2.9 g/L in cows.

The physiological range for the daily saliva production of an adult cow is 100 – 190 L/d (Schmidt-Nielsen, 1997), which leads to a daily potassium content in saliva of 15.6-551 g/d. In the model, the average secretion of potassium with saliva during 24 h is 47.08 g.

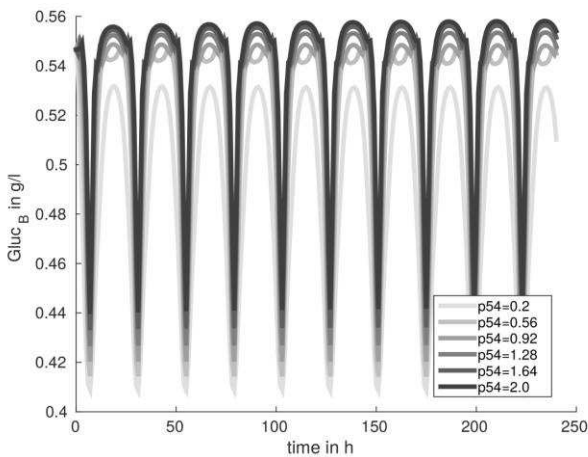
Figure 3: *DMI* is varied via p_{54} , the variation parameter for the default *DMI*, in steps of 0.36 between 0.2 and 2.0. When p_{54} is 0.2, 0.56, 0.92, 1.28, 1.64 and 2.0 g/h the cow is consuming 2340, 6552, 10764, 14976, 19188 and 23400 g *DMI*, respectively.



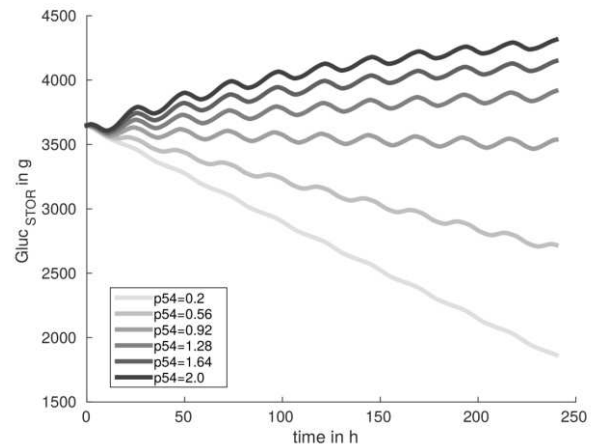
3a: With increasing *DMI*, potassium excretion with urine (K_{URIN}) increases.



3b: The higher *DMI* is the more potassium is stored in the tissue component (K_{TISS}). For lower *DMI* the stored K is consumed.



3c: With increasing *DMI* one observes increasing values of $Gluc_B$ mainly in the peak values.



3d: The higher *DMI* is the more glucose is stored in the storage component ($Gluc_{STOR}$). For lower *DMI* the stored glucose is consumed.

In the study of Christinaz and Schatzmann (1972), cows were found with erythrocyte potassium concentrations, corresponding to the model component K_{ICF} , between 7 and 70 mmol/L. In this study, most individuals were found to have an erythrocyte potassium concentration of around either 20 mmol/L or 50 mmol/L, based on genetic variation with no breed influence (Christinaz, 1972). In the data provided for model development we observed a similar tendency. We decided to model the so called low-potassium cows with an erythrocyte potassium concentration around 20 mmol/L. By interchanging K_{TISS} (fig. 2c) with K_{ECF} loses 27.9 g potassium during the 10 days simulation period.

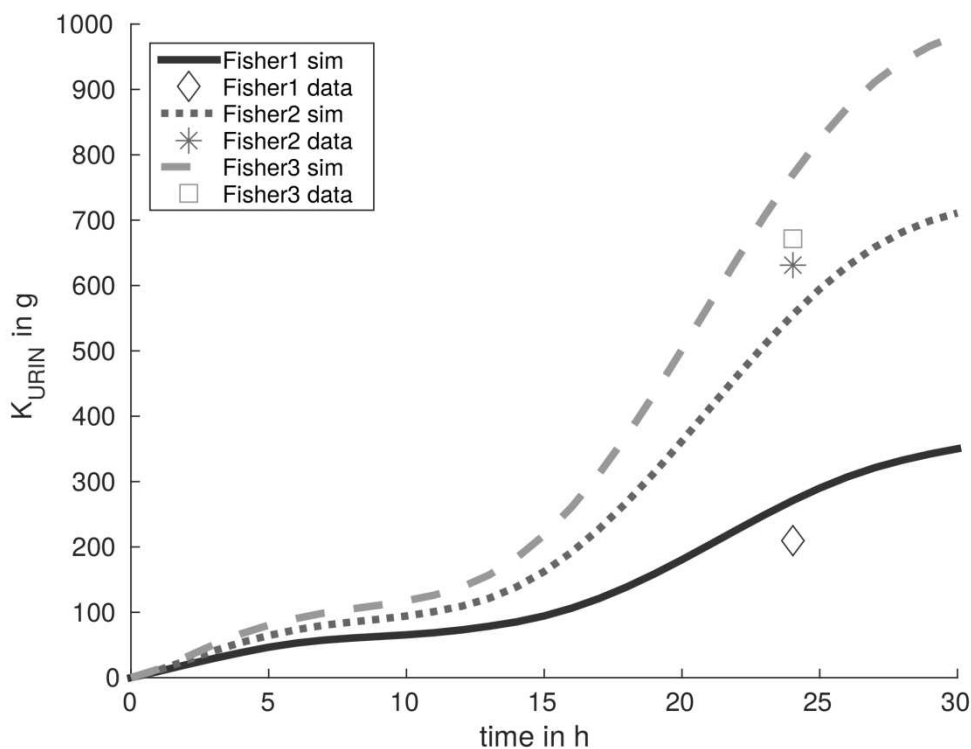


Figure 4: Simulation outcome for model components K_{URIN} (K in urine) under the condition as performed in the study of Fisher et al. (1994). Fisher et al. (1994) studied potassium excess in lactating dairy cows, feeding total mixed rations with 1.6%, 3.1% and 4.6% potassium. According to their experimental study, the parameters p_{54} (% DMI), p_{55} (milk production in L/h) and p_{56} (potassium in DMI) were varied. Fisher 1 ($p_{54} = 1.97$, $p_{55} = 1.32$, $p_{56} = 0.016$); Fisher 2 ($p_{54} = 2.03$, $p_{55} = 1.31$, $p_{56} = 0.031$), Fisher 3 ($p_{54} = 1.91$, $p_{55} = 1.24$, $p_{56} = 0.046$).

In figure 2c, one can observe the accumulated excretion of potassium with K_{URIN} . Within the 10 days simulation period the cow excreted in average 130.6 g potassium per day, which exceeds the ingested amount of 126.3g per day by 4.3 g. This potassium loss is fed mainly from K_{TISS} .

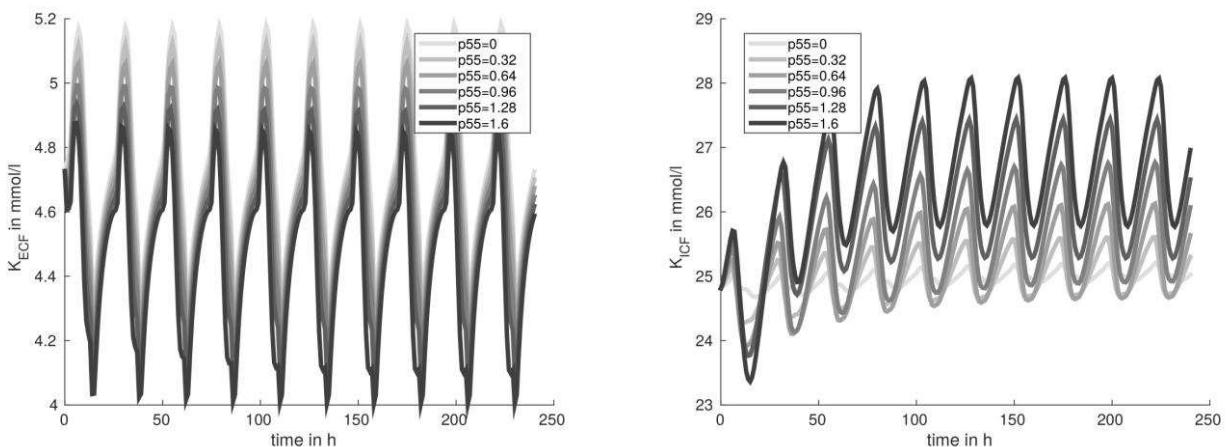
$Gluc_{FEED}$ (fig. 2a) is 8.5 % of DMI in the default condition, representing carbohydrates convertible to glucose. Its dynamic follows the dynamic of DMI . In $Gluc_{PROD}$ (fig. 2c), glucogenic substances are converted to glucose and nourish blood glucose ($Gluc_B$, fig. 2d) and are stored in $Gluc_{STOR}$ (fig. 2c), whereby the loss in the 10 days simulation period was 4.6 g, representing a relatively balanced nutrition.

Due to the model construction pH is very stable even if the input is varied within maximal physiological values, that is pH can be at most 7.43 if metabolic activity is zero, and minimum values will not fall below pH = 7.34 if DMI is above 40 kg.

Experiment 1: Variation of DMI

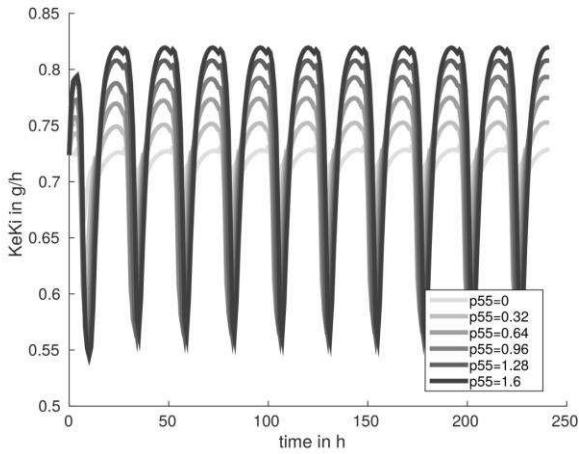
In this experiment, DMI is varied by varying p_{54} , the variation factor of the default DMI , in steps of 0.36 between 0.2 and 2.0 g/h. When p_{54} is 0.2, 0.56, 0.92, 1.28, 1.64 and 2.0 g/h, the cow is consuming 2340, 6552, 10764, 14976, 19188 and 23400 g DMI , respectively. The recommendations by the National Research Council (2001) describe a maximum feed intake of up to 4 % bodyweight, which would be 24 kg DMI for the cow modeled here.

Figure 5: Milk production is varied with p_{55} (milk production in L/h) from 0 to 1.6 L/h in steps of 0.32 L/h. When p_{55} is 0, 0.32, 0.64, 0.96, 1.28 and 1.6 L/h the cow produces 0, 7.7, 15.4, 23.0, 30.7 and 38.4 L milk per day, respectively.

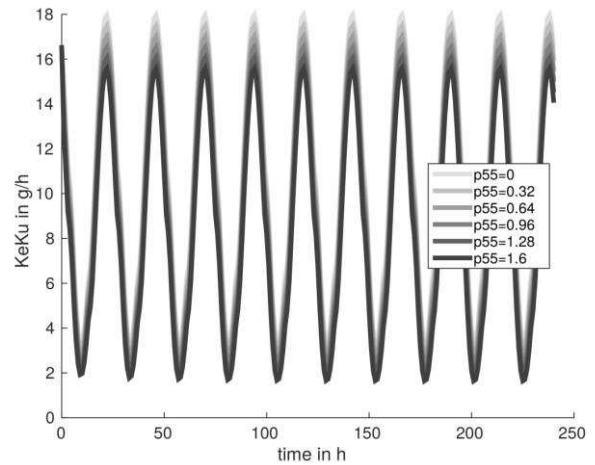


5a: The amplitude of K_{ECF} increases with increasing milk yield.

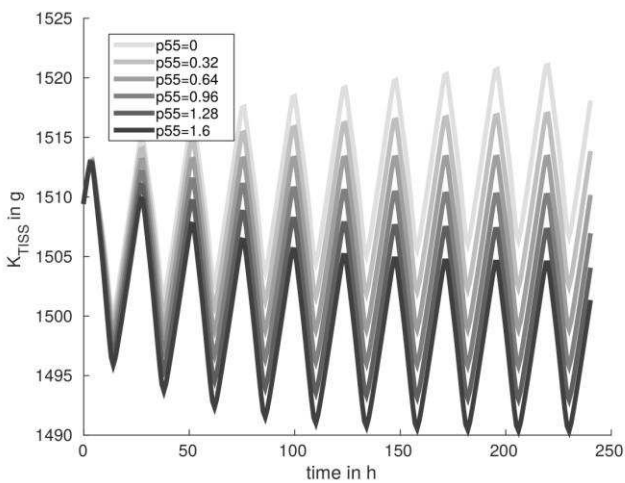
5b: The mean values and amplitude of K_{ICF} increase with increasing milk yield.



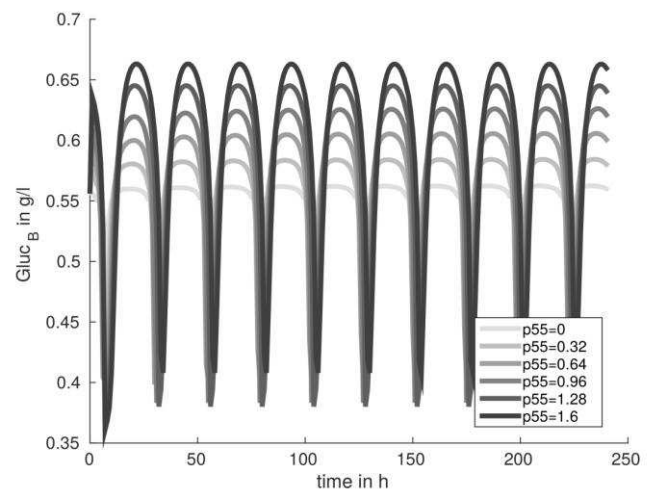
5c: The amplitude of the rate $KeKi$ (K flow from extracellular- to intracellular blood fluid) increases with increasing milk production.



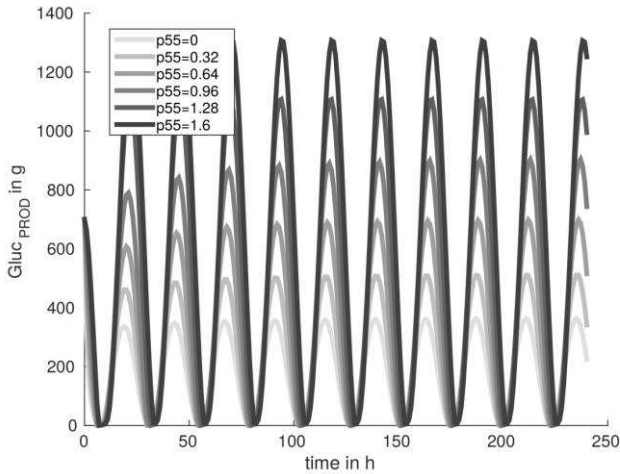
5d: With increasing milk production, the amplitude of the rate $KeKu$ (K flow from extracellular blood fluid to urine) decreases and less potassium is excreted with urine.



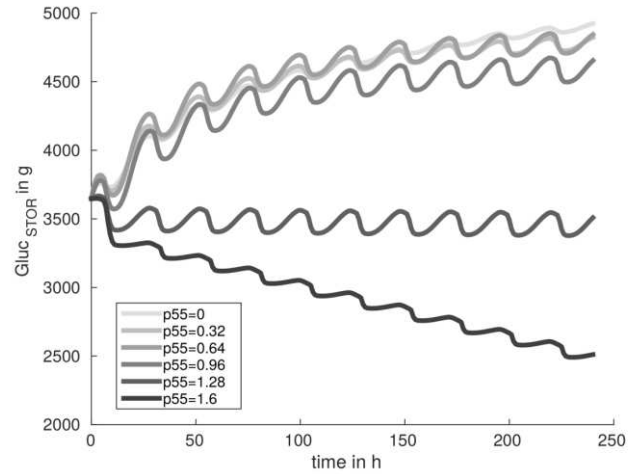
5e: With increasing milk production less potassium is stored and one observes a decrease of amplitude and values of K_{TISS} .



5f: With increasing milk production $Gluc_B$ increases its peak values.



5g: With increasing milk production, the amplitude of $Gluc_{PROD}$ increases.



5h: With increasing milk production the model component $Gluc_{STOR}$ decreases. The lower milk production is the more glucose is stored. For higher milk production the storage is consumed.

Figure 3a shows the simulation outcome for the accumulated model component K_{URIN} , under varying DMI . With increasing DMI , an increasing total amount of potassium is taken up and excreted with urine, which coincides with the observations made by Youn and McDonough (2009).

Figure 3b shows the simulation result for the model component K_{TISS} with varied DMI . With increasing DMI intake, more potassium is stored in the storage component K_{TISS} due to the fact that the cow is ingesting more potassium than she needs.

In figure 3c, one can observe the simulation outcome for the model component $Gluc_B$ under varying DMI . The peak blood glucose values are increasing with increasing DMI and thus increasing glucose intake. Blood glucose values stay in their physiological range (see section **Mechanisms**).

In figure 3d one can observe the simulation outcome for the model component $Gluc_{STOR}$ for varying DMI . The dynamics of the glucose storage component is similar to the potassium storage component K_{TISS} . Glucose supply above the default condition fills up the storage. When DMI is below the default condition, glucose storage is decreasing while glucose is shifted to $Gluc_B$ to be available for maintenance and production.

Experiment 2: Variation of K_{FEED}

Fisher et al. (1994) studied potassium excess in lactating dairy cows, feeding total mixed rations with 1.6%, 3.1% and 4.6% potassium. According to their experimental study, the parameters p_{54} (% DMI), p_{55} (milk production) and p_{56} (potassium in DMI) are varied. Fig. 4 shows data of potassium in

urine from the field experiment and model simulations under similar conditions. Note that, these data was not used for model development or parameter fitting. With additional data, e.g. bodyweight of cows or amount of glucogenic substances in the food, the model could be adapted more precisely to the experimental conditions and hence be more useful for making predictions.

Experiment 3: Milk Production

Milk production is activated by setting $p_{55} > 0$ L/h. In the present experiment the value of p_{55} is varied as follows: 0, 0.32, 0.64, 0.96, 1.28 and 1.6 L/h leading to the production of 0, 7.7, 15.4, 23.0, 30.7 and 38.4 L milk per day, respectively. DMI is 200% of the default condition and $Gluc_{FEED}$ is 20% of DMI , all other parameters kept their values according to the default condition. This is in the range of the recommendations for nutrition of cows in milk (National Research Council, 2001).

Figures 5a-h show the simulation outcome in this experiment. In fig. 5a and 5b, one can observe the simulation outcome for the model components K_{ECF} and K_{ICF} , respectively. With increasing milk production, increasing amounts of potassium are demanded directly from K_{ECF} . In the simulations we notice that, with an increasing demand for potassium, K_{ECF} is getting marginally lower but kept in its physiological range and not dropping into hypokalemic regimes. One can observe a higher amplitude for K_{ICF} and K_{ECF} , representing a higher activity of the whole metabolism and, in particular, of potassium metabolism. K_{ICF} is increasing due to higher amplitudes in glucose metabolism. Insulin is rising and, subsequently, the rate K_{eki} (fig. 5c) at which potassium moves from extracellular to intracellular space, is increasing. This mechanism has been shown for splanchnic tissue and for skeletal muscle cells (DeFronzo, 1980).

In the simulation outcome for the $KeKu$ rate (fig. 5d) one can observe the potassium moving from extracellular space to urine in g/h. With increasing milk production, less potassium is excreted with the urine. This mechanism was included to reduce potassium excretion as far as possible in the case of milk production, to have more resources for the milk.

Figures 5f, 5g and 5h show the simulation outcome for the components from glucose metabolism, $Gluc_B$, $Gluc_{PROD}$ and $Gluc_{STOR}$, for a lactating cow. The $Gluc_B$ simulation result shows a higher level for increasing milk production and thus for a more active metabolism, which is the same effect as already described for the variation of DMI (fig. 3c). With 20% DMI the glucose input via $Gluc_{FEED}$ is high enough to meet the demand of higher milk production of 38.4 L/d. This submodel is a solid start to progress dynamic modelling of glucose metabolism for lactating ruminants.

CONCLUSION

We have introduced a mathematical model for the potassium balance in lactating and non-lactating dairy cows, including an important submodel for glucose metabolism. The simulation outcomes for the default condition as well as for three different experiments show a satisfying consistency with literature knowledge.

In particular, a comparison of model simulations with data from Fisher et al. (1994) shows that the model can reproduce the trends in these data, although this data was not used during the modeling process. This validates our approach.

We have used a number of conditions, e.g. body weight and default feed intake, given from a clinical study conducted by the Clinic for Ruminants of Freie Universität Berlin. However, we have not shown the data in direct comparison to the simulation results because of their large inter-individual variability. (See Plöntzke et al. (2013) for our preliminary modeling approach including plots of the data.)

For future work it seems promising to extend the model by integrating the dynamics of other minerals such as sodium, calcium and magnesium. Using these minerals would allow for a refinement of the renal excretion, which is at a relatively coarse modeling level until now. We also aim at modeling glucocorticoid therapy, a typical veterinarian intervention in cows related to potassium metabolism. In addition, we would like to validate the model with more data.

ACKNOWLEDGMENTS

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Table 1. Components and units of the herein presented model for potassium balance in dairy cows. Initial values are given for the default condition.

Component	Explanation	Initial Value	Unit
<i>DMI</i>	dry matter intake	487.5	g / h
<i>K_{FEED}</i>	potassium uptake with the diet	5.5429	g / h
<i>K_{ECF}</i>	potassium in the extracellular blood fluid	0.1751	g / L
<i>K_{ICF}</i>	potassium in the intracellular blood fluid	0.8973	g / L
<i>K_{URIN}</i>	potassium excreted with urine, accumulated	0	g
<i>K_{GIT}</i>	potassium in the gastrointestinal tract	43.1366	g
<i>K_{TISS}</i>	potassium in tissues except blood and bone	1509.6	g
<i>K_{SAL}</i>	potassium in saliva	4.5382	g
<i>K_{MILK}</i>	potassium in milk, accumulated	0	g
<i>Insulin</i>	insulin in blood	21.8533	μU/mL
<i>Gluc_{FEED}</i>	uptake of glucogenic substances with feed	41.6325	g / h
<i>Gluc_{PROD}</i>	internal pool of produced glucose	34.03	g
<i>Gluc_B</i>	glucose in blood	0.5466	g / L
<i>Gluc_{STOR}</i>	stored glucose in the tissues	3647.7	g
<i>Metabolic Activity</i>	virtual compound	6.2489	-
<i>pH</i>	pH of blood	7.3438	-

Table 2. Parameters and units.

(Remark: In the numbering three numbers are not assigned, so the absolute number of parameters is 63, although the last parameter is p_{66} .)

Parameter	Value	Unit	Explanation
p_1	40.4	g/h	Hill threshold for $Gluc_{FEED}$ in the rate $GsGb$
p_2	1600.0	g	Hill threshold for K_{TISS}
p_3	22.0	$\mu\text{U/mL}$	Hill threshold for Insulin
p_4	0.0001783	L/h	Clearance factor for K_{ECF}
p_5	0.563	g/h	Basic rate of potassium in $KiKe$
p_6	0.051	1/h	Scaling factor for the rate $KeKu$
p_7	0.925	g/h	Threshold for glucose in the rate $GsGb$
p_8	0.5994	g/h	Basic rate of potassium in $KeKi$
p_9	0.4016	g/h	Scaling factor for Hill function in the rate $KeKi$
p_{10}	1400.0	g	Subtrahend for better functioning of the Hill function for K_{TISS} with a large threshold
p_{12}	0.0105	$\text{L/g} \cdot 1/\text{h} \cdot \text{mL}/\mu\text{U}$	Scaling factor for the rate $GsGb$
p_{13}	6.08	-	Scaling factor for Hill function in the rate $KeKu$
p_{14}	0.15639932	g/L	Hill threshold for K_{ICF}
p_{15}	32.0	g	Hill threshold for K_{GIT}
p_{16}	10.0	-	Scaling factor for Hill function in the rate $KeKu$
p_{17}	16.0	L/h	Basic rate of glucose in the rate $GsGb$
p_{18}	0.0223	L/g	Basic rate of potassium in the rate $KeKs$
p_{19}	0.1373	-	Scaling factor for Hill function in the rate $KiKe$
p_{20}	7.38	-	Hill threshold for pH
p_{21}	0.1085	-	Scaling factor for Hill function in the rate $KeKi$
p_{22}	0.25	g/L	Hill threshold for K_{ECF}
p_{23}	0.58649745	g/L	Hill threshold for K_{ICF}

p_{24}	0.1962811466	g/L	Hill threshold for K_{ECF}
p_{25}	6.6085	L/h	Scaling factor for the rate $KeKt$
p_{26}	49.0279	L/h	Scaling factor for the rate $KtKe$
p_{27}	0.232634885	g/L	Threshold for K_{ECF}
p_{28}	25.0	L/h	Fraction of $Gluc_B$ for body use
p_{29}	0.11729949	g/L	Hill threshold for K_{ECF}
p_{30}	0.95	-	Fraction of K_{FEED} passing to K_{GIT}
p_{31}	0.353	1/h	Fraction of K_{GIT} absorbed to K_{ECF}
p_{32}	1.31	1/h	Fraction of K_{SAL} passing to K_{GIT}
p_{33}	0.07819966	g/L	Hill threshold for K_{ECF}
p_{35}	100.0	g	Hill threshold for $Gluc_{STOR}$
p_{36}	1.0	L/h	Hill threshold for milk production
p_{38}	1509.6	g	Hill threshold for K_{TISS}
p_{39}	30.0	1/h	Basic rate of glucose in the rate $GpGb$
p_{40}	0.01	g/L	Hill threshold for K_{ECF}
p_{41}	20.0	L/h	Factor for insulin clearance
p_{42}	4.5	1/h	Factor for DMI dependant stimulation of <i>Metabolic activity</i>
p_{43}	10.0	g/h	Hill threshold for DMI
p_{44}	1.2	1/h	Clearance factor for Metabolic activity
p_{45}	3.0	1/h	Basic stimulation of Metabolic activity
p_{46}	0.0854	-	Fraction of glucose and glucogenic substances in DMI
p_{47}	72.0	g/L	Glucose for milk production
p_{48}	0.08	-	Glucose directly absorbed from $Gluc_{FEED}$ to $Gluc_B$
p_{49}	800.0	$\mu U/mg \cdot L/h$	Scaling factor for $Gluc_B$ influencing insulin production
p_{50}	0.4	g/l	Hill threshold for $Gluc_B$
p_{51}	0.1	1/h	Basic rate of glucose in the rate $GpGs$

p_{52}	1.4	g/L	Scaling factor for the rate $KeKm$
p_{53}	0.01	L/g	Scaling factor for K_{ECF} influencing urine excretion of potassium
p_{54}	1.0	g/h	For variation of feed intake
p_{55}	0.0	L/h	Milk production
p_{56}	0.01137	-	Potassium content in DMI
p_{57}	3800.0	g	Hill threshold for $Gluc_{STOR}$
p_{58}	0.01	g/L	Hill threshold for $Gluc_B$
p_{59}	1.0	l/h	Fraction of $Gluc_{PROD}$ for body use
p_{60}	2.0	g/h	Basic rate of glucose in the rate $GsGp$
p_{61}	5.0	g/h	Hill threshold for $Gluc_{FEED}$
p_{62}	1.0	L/h	Hill threshold for milk production
p_{63}	800.0	g/h	Increasing factor for the rate $GsGb$ during milk production
p_{64}	0.2	L/h	Hill threshold for milk production
p_{65}	0.3	g/L	Hill threshold for $Gluc_B$
p_{66}	1.4	h/L	Scaling factor for reduction of glucose body use during milk production

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