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Modeling potassium balance in dairy cows

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Abstract

Potassium is fundamental for cell functioning including signal transduction, acid-base and water metabolism. Since diet of dairy cows is generally rich in potassium, hypokalemia was not in the focus of research for long time. Furthermore, hypokalemia was not frequently diagnosed because blood potassium content is difficult to measure. In recent years, measurement methods have been improved. Nowadays hypokalemia is increasingly diagnosed in cows with disorders such as abomasal displacement, ketosis or down cow syndrome, calling for intensified research on this topic. In this report we describe the development of a basic mechanistic, dynamic model of potassium balance based on ordinary differential and algebraic equations. Parameter values are obtained from data of a clinical trial in which potassium balance and the influence of therapeutic intervention in glucose and electrolyte metabolism on potassium balance in non-lactating dairy cows were studied. The model is formulated at a high abstraction level and includes information and hypotheses from literature. This work represents a first step towards the understanding and design of effective prophylactic feed additives and treatment strategies.

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1 Introduction

Potassium is a monovalent cation with little tendency to form complexes. In the organism, its action is mainly associated with the translocation of charges. It is fundamental for cell functioning being involved in signal transduction, acid-base- and water metabolism. Potassium is uptaken continuously with the diet. After resorption from the intestinal tract it distributes dynamically between intra- and extracellular space in all tissues. In interplay with natrium it determines cellular excitability [11]. Its main excretion pathway is via the kidneys. However, the knowledge about detailed mechanisms and regulation of potassium balance in mammals is still incomplete [27].

High performing dairy cows require a particular composition of nutritional ingredients adapted to their production status. The optimal dimensioning of minerals in diet including potassium is indispensable for the prevention of disbalances. Current nutritional recommendations propose a diet low in potassium before calving [8]. Depending on soil and fertilisation, diet of dairy cows is generally rich in potassium. Thus for a long time hypokalemia was not in the focus of research. Furthermore hypokalemia is not frequently diagnosed because the measurement of serum potassium content needs special attention. In cattle and other mammals serum potassium concentration is maintained in the narrow range between 3.5 and 5.8 mmol/l [21]. While the majority of potassium is located intracellular, little cell damages may lead to large overestimation of serum potassium content [21]. In recent years, measurement methods have been improved, and hypokalemia has increasingly been diagnosed in cows in conjunction with metabolic and mineralic disbalances, abomasal displacement, ketosis and recumbency [12, 15, 20], calling for intensified research on this topic.

Potassium balance closely interacts with glucose and electrolyte metabolism [9], in which post-partum veterinary treatments frequently intervene. Administration of corticosteroids or dextrose infusions have been shown to favour hypokalemia [15, 20, 9].

In cooperation between veterinarians and mathematicians we set out to develop a mechanistic model for potassium balance in dairy cows. We focus on the whole organism instead of cellular level, with a clear emphasis on developing a mechanistic functional model, since data in this field is usually too inhomogeneous to reproduce it exactly. To our knowledge, no one has published work that explicitly describes a bio-mathematical, mechanistic model of potassium balance in dairy cows, or in another livestock species, yet. Mathematical modeling of the involved mechanisms gives insight into the underlying biological processes and enables predictions. The long-term goal of developing such a model is to assist development of feed additives and effective treatment strategies, to support herd management decisions as well as to optimize individual cow management, and to reduce costs for dairy farmers by an overall better performance and by decreasing expenses for drugs.

2 Model Development

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

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

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 .

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 8 ODEs, 4 algebraic equations and 33 parameters. The mechanisms of our model are pictured in

	Component	Explanation	Unit
y_1	K_{ECF}	potassium in the extracellular blood fluid	mmol/l
y_2	K_{ICF}	potassium in the intracellular blood fluid	mmol/l
y_3	K_{URIN}	potassium excreted with urine, accumulated	g
y_4	K_{GIT}	potassium in the gastro intestinal tract	g
y_5	K_{TISS}	potassium in tissues except blood and bone	g
y_6	K_{SAL}	potassium in saliva	g
y_7	K_{EX}	total potassium excreted	g
y_8	$Insulin$	insulin in blood	$\mu\text{U/ml}$
y_9	pH	ph of blood	-
y_{10}	$Glucose$	glucose in blood	mmol/l
y_{11}	K_{FEED}	potassium content in the diet	g
y_{12}	$Metabolic\ Activity$	virtual compound	-

Table 1: Components and units of the herein presented model for potassium balance in dairy cows.

dissolved. Blood volume calculation is made on the base of 55 ml blood per kg bodyweight as reported by Reynolds et al. [19]. The bodyweight is a cow-specific parameter (p_{10}) given from experimental data. The intra- and extracellular volume of blood tissue is calculated with the help of the hematocrit, which represents the volume of the cellular components in the blood. Hematocrit (p_{17}) is a cow-specific parameter obtained from experimental data.

2.3 Mechanisms

Potassium balance is determined by dietary potassium content, its resorption, 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.

2.3.1 Potassium Uptake

Feed intake In our model the ingested amount of potassium is represented by K_{FEED} , the driving force of the model. The model cow ingests feed between 7:00 am and 11:00 pm, so feed ingestion occurs over 16 hours/day. Between 23 pm and 7 am the cow does not ingest any feed. From the clinical study potassium uptake was given with 132.8 g per day.

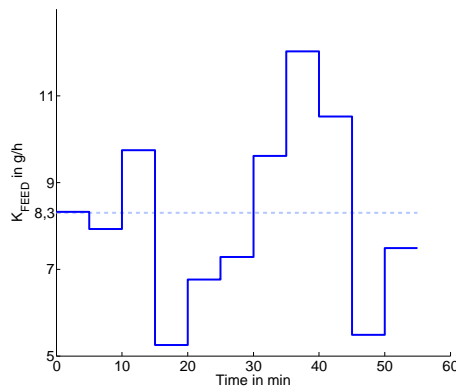


Figure 2: Randomized (solid line) and continuous (dashed line) K_{FEED} over an exemplary time period

To simulate K_{FEED} one can choose between a continuous and a randomized feed intake (see Fig. 2). If the input component K_{FEED} is randomized the model reproduces an oscillatory behaviour of the components similar to the experimental data, see e.g. Fig. 5(a). For randomized feed intake, every 5 minutes a random value is created using the MATLAB command *randn* with a standard deviation of 3 g and a mean value of 8.3 g/h to achieve a potassium uptake of 8.3 g/h over 16 hours which is equivalent to 132.8 g/d.

If the input component K_{FEED} is modeled constantly we can observe the mechanisms more clearly. For continuous feed intake under default condition 8.3 g/h are ingested. To conduct simulations with different amounts of potassium, the hourly potassium intake can be varied.

$$\mathbf{K}_{FEED}: y_{11} = \begin{cases} 8.3, & \text{continuous option} \\ 8.3 + 3 \cdot \xi, & \text{with } \xi \text{ random variable with standard normal distribution} \end{cases}$$

Resorption The resorption of potassium from diet is up to 97% in the cow and increases with increasing amount of potassium in the rumen [18]. In our model 95% of K_{FEED} is passing to the gastrointestinal tract K_{GIT} with the rate $KfKg$.

$$KfKg = p_{30} \cdot y_{11}$$

Detailed mechanisms of potassium resorption are different throughout the different segments of the gastrointestinal tract. We pool this whole system in one component K_{GIT} . In K_{GIT} potassium accumulates and is resorbed to K_{ECF} with the rate $KgKe$.

$$KgKe = p_{31} \cdot y_4$$

In addition potassium is transported with saliva to K_{GIT} with the rate $KsKg$.

$$KsKg = p_{32} \cdot y_6$$

$$\mathbf{K}_{GIT}: \frac{d}{dt}y_4 = KfKg - KgKe + KsKg$$

2.3.2 Metabolic Components

Potassium balance closely interacts with the metabolism. 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 represented by the components *Glucose*, *Insulin*, *Metabolic activity* and *pH*.

Glucose Metabolism In vivo, insulin is secreted from pancreatic beta cells in response to elevated blood levels of nutrients such as glucose or amino acids. It causes glucose uptake into cells of liver, muscle and fat tissue, 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 [27]. Glucose concentration in blood tissue is modeled with an algebraic equation.

$$\mathbf{Glucose}: y_{10} = p_1 + (y_{11} - 8.3) \cdot p_{28}$$

The scaled K_{FEED} is added to a cow-specific mean value p_1 received from experimental data, counting for feed dependency of blood glucose. *Insulin* is modeled with a growth-decay equation, whereby the growth depends on *Glucose*.

$$\mathbf{Insulin}: \frac{d}{dt}y_8 = \left(\frac{p_3}{p_1} \cdot y_{10} - y_8\right) \cdot p_2$$

Thus, in our simulation the curve for *Insulin* is similar to *Glucose*, but slightly delayed in time.

Acid-base Metabolism *Metabolic activity* is a dimensionless value, which depends on *Glucose* and the amount of potassium in K_{GIT} , because potassium is uptaken together with all other nutritional components.

$$\text{Metabolic activity: } y_{12} = 0.1 \cdot y_4 + y_{10}$$

The *Metabolic activity* component has been introduced with the purpose to model pH dependency of metabolism. The *pH* has a cow-specific mean value, received from experimental data, from which we subtract $\frac{1}{40}$ of *Metabolic activity* to obtain a decaying *pH* when *Metabolic activity* is high and vice versa.

$$\text{pH: } y_9 = 7.5 - \frac{y_{12}}{40}$$

2.3.3 Potassium Homeostasis

Potassium homeostasis in the cow is characterized by a consistent flow of potassium cations between different compartments and tissues, in our 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 [21]. High serum potassium levels (hyperkalemia) lead to heart arrythmia and other severe dysfunctions in excitable cells [23]. Low serum potassium levels (hypokalemia) lead to a lack of motility and excitability of cells [22]. In our model after resorption 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 In our model the component K_{SAL} represents the amount of potassium in the saliva. Potassium in K_{SAL} is nourished by K_{ECF} with the rate $KeKs$.

$$KeKs = p_{18} \cdot y_1$$

Depending on diet, cows produce up to 138-179 l saliva per day [24] with a varying content of potassium [26]. Saliva is swallowed with the feed to the rumen, in the model from K_{SAL} to K_{GIT} with the rate $KsKg$.

$$K_{SAL}: \frac{d}{dt}y_6 = \frac{KeKs}{con} - KsKg,$$

where $con = \frac{\frac{1 \text{ mol}}{39.0983 \text{ g}}}{p_{10} \cdot (1-p_{17}) \cdot 55 \cdot 10^{-3} \cdot \frac{\text{l}}{\text{kg}}} \approx \frac{465}{\frac{p_{10}}{\text{kg}} \cdot (1-p_{17})} \frac{\text{mmol}}{\text{l} \cdot \text{g}}$ is the cow-specific conversion factor from g to mmol/l in K_{ECF} , which is calculated using the molar mass of potassium ($39.0983 \frac{\text{g}}{\text{mol}}$) and the assumption that the cow has 55 ml blood per kg body weight (see 2.2).

Cellular Uptake In our model potassium is shifted from K_{ECF} to K_{ICF} with the rate $KeKi$, which is basically the constant parameter p_8 . Under certain conditions $KeKi$ is modified as follows. If *Insulin* rises and passes a cow-specific mean value (p_3), it enhances cellular uptake with the rate p_9 . If *pH* is above the cow-specific mean value p_{20} , $KeKi$ is increased by p_{21} . 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 K_{ECF} from dropping more.

$$KeKi = (p_8 + p_9 \cdot H^+(y_8, p_3; 10)) \cdot H^+(y_1, p_{33}; 2) \cdot (1 + p_{21} \cdot H^+(y_9, p_{20}; 10))$$

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} . If K_{ECF} drops under p_{29} , up to 100% more of potassium drifts from K_{ICF} to K_{ECF} . 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} .

$$KiKe = (1 + H^-(y_1, p_{29}; 10)) \cdot p_5 \cdot (1 + H^-(y_9, p_{20}; 10)) \cdot H^+(y_2, p_{23}; 2) \cdot (1 + p_{19} \cdot H^+(y_2, p_{14}; 2))$$

$$\mathbf{K}_{ECF}: \frac{d}{dt}y_1 = con \cdot (KgKe - KeKu) - KeKt + KtKe + KiKe - KeKi - KeR - KeKs$$

$$\mathbf{K}_{ICF}: \frac{d}{dt}y_2 = (KeKi - KiKe) \cdot con_{vol}$$

where $con_{vol} = \frac{1-p_{17}}{p_{17}}$ is the conversion factor for volume of extracellular fluid to volume of intracellular fluid, which is calculated using the cow-specific hematocrit p_{17} .

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. [1] studied the potassium content of different tissues in cattle. They found a mean potassium content of 3 g per kg bodyweight, which we used to calculate the initial value for K_{TISS} , representing the reservoir for 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 $K_{GIT} > p_{15}$.

Potassium leaves K_{TISS} to K_{ECF} with the rate $KtKe$ only when $K_{GIT} < p_{15}$. $KtKe$ is intended to increase when the value of K_{ECF} decreases, so the current rate $KtKe$ is a multiple of $p_{27} - K_{ECF}$. If K_{TISS} has diminished by 1% $KtKe$ rate 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 for the extracellular fluid.

$$KeKt = H^+(y_4, p_{15}; 10) \cdot p_{25} \cdot y_1$$

$$KtKe = H^-(y_4, p_{15}; 10) \cdot p_{26} \cdot (p_{27} - y_1) \cdot H^+(y_5, 0.99 \cdot y_5(0); 100)$$

$$\mathbf{K}_{TISS}: \frac{d}{dt}y_5 = \frac{1}{con} (KeKt - KtKe)$$

2.3.4 Potassium Excretion

Potassium is excreted mainly with urine [26], in our model K_{URIN} , with the rate $KeKu$. In addition, saliva, milk and sudor contain remarkable amounts of potassium. In our model potassium content of saliva is represented by K_{SAL} (see 2.3.3 for detailed mechanism). Potassium in sudor is fed by K_{ECF} with the rate KeR .

$$KeR = p_4 \cdot y_1$$

Milk did not play a role in the development of the model in its present form, since the used dataset has been collected in non lactating cows.

It is still not fully understood how serum potassium excretion is regulated exactly. There are known mechanisms and evidence based hypotheses. In hyperkalemia, potassium excretion is regulated by aldosterone [17], a mineralocorticoid from the cortex of the adrenal gland. In our model aldosterone is activated when K_{ECF} rises above $p_{24} = 5$ mmol/l by adding $p_{13} \cdot 100\%$ on $KeKu$ and thereby enhancing excretion. There is strong evidence for a feedforward regulation of potassium excretion, because an increase in excretion can be observed without significant rise in serum potassium [10]. There are three supposed mechanisms for feedforward regulation: (1) a gut receptor, which enhances potassium excretion after a potassium rich meal; (2) a portal vein receptor, which is confirmed to be bumethanid sensitive in the rat and (3) regulation from the central nervous system [14, 10]. In our model we account for feedforward regulation via a direct dependency of $KeKu$ on the actual value of K_{GIT} . Furthermore $KeKu$ prevents K_{ECF} from growing above life-threatening levels as for $K_{ECF} > 8$ mmol/l [4] a Hill function increases the excretion via urine.

$$\mathbf{K}_{URIN}: \frac{d}{dt}y_3 = KeKu$$

$$KeKu = (1 + p_{13} \cdot H^+(y_1, p_{24}; 5)) \cdot p_6 \cdot y_4 \cdot (1 + p_{16} \cdot y_1 \cdot H^+(y_1, p_{22}; 10))$$

To calculate the amount of total potassium excreted we introduce the component K_{EX} . This component simply consists of the sum of the rates with which potassium is excreted, i.e. with urine, sudor, and feces.

$$K_{EX}: \frac{d}{dt}y_7 = KeKu + \frac{KeR}{con} + 0.05 \cdot y_{11}$$

3 Simulation Results

In order to revise the model mechanisms we conducted experiments and evaluated the simulation outcomes quantitatively. The experimental data from the clinical study are noisy and differ between individual cows. Especially the values for K_{ICF} , the measured potassium content in erythrocytes, show a strong interindividual variability. This phenomenon has been described by Christinaz et al. [2], who found it to be based on genetic variation with no breed influence. In the same study [2], cows were found with erythrocyte potassium concentrations between 7 and 70 mmol/l, while most individuals were found to have an erythrocyte potassium concentration of around either 20 mmol/l or 50 mmol/l. In our study animals we observe a similar tendency. Furthermore, experimental data of insulin show strong interindividual variations, too. Therefore, some parameters have general values which stay constant for all cows, whereas some parameters were set individually for each cow (see Table 2 in Appendix).

To solve the differential equations we use a linearly implicit Euler method with extrapolation implemented in the code LIMEX [6]. In section 3.1 we first present outcomes from the simulation of potassium balance without intervention. To verify the mechanistic functions of the model, in section 3.2.1 we vary the potassium intake by simulating the administration of a potassium bolus as well as varying the feed potassium content as previously studied in field feeding experiments.

3.1 Potassium Balance

In this section we present the simulation outcomes including experimental data from one of the six study cows. We present two kinds of simulation: Every component will be explained and shown under both randomized and constant input conditions. The starting point of simulations ($t = 0$) equates 6:00 am.

3.1.1 Potassium Uptake

K_{FEED} (Figure 3(a)) is input and driving force of the model. The clinical study involved a potassium intake of 132.8 g/d. This corresponds to a diet with 1.13 % potassium in dry matter (DM), a sufficient to elevated potassium supply for the non lactating study animals. Simulation of K_{FEED} can be conducted randomized or constant, in both cases the mean potassium uptake is supposed to be 8.3 g/h over 16 h (for explanation see 2.3.1).

The trend induced by K_{FEED} continues through the whole system. In Figure 3(b) we observe the simulation outcome for the component K_{GIT} , representing the potassium content of the gastrointestinal tract. As potassium accumulates herein we observe an accumulation as long as the cow constantly ingests feed and a decline when no feed is ingested.

3.1.2 Metabolic Components

Simulation outcomes for the metabolic components are presented in Figure 4. For *Glucose* (a) and *Insulin* (b) experimental data are extremely noisy. Furthermore, the interindividual variability for insulin in the experimental data is very high. As our aim for the metabolic components was to obtain their mechanistic influence on potassium metabolism, we model mechanisms with little details (see 2.3.2). *Glucose* depends on the feed intake K_{FEED} and *Insulin* follows *Glucose* slightly delayed in time. The simulation of the virtual component *Metabolic activity* is similar to K_{GIT}

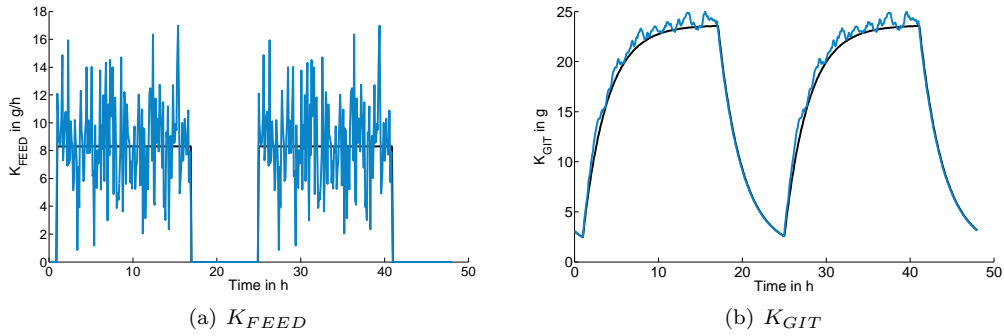


Figure 3: Simulation outcome for potassium uptake.

on which it mainly depends. Simulation outcome for pH is contrary to *Metabolic activity*. When *Metabolic activity* is high pH decays and vice versa.

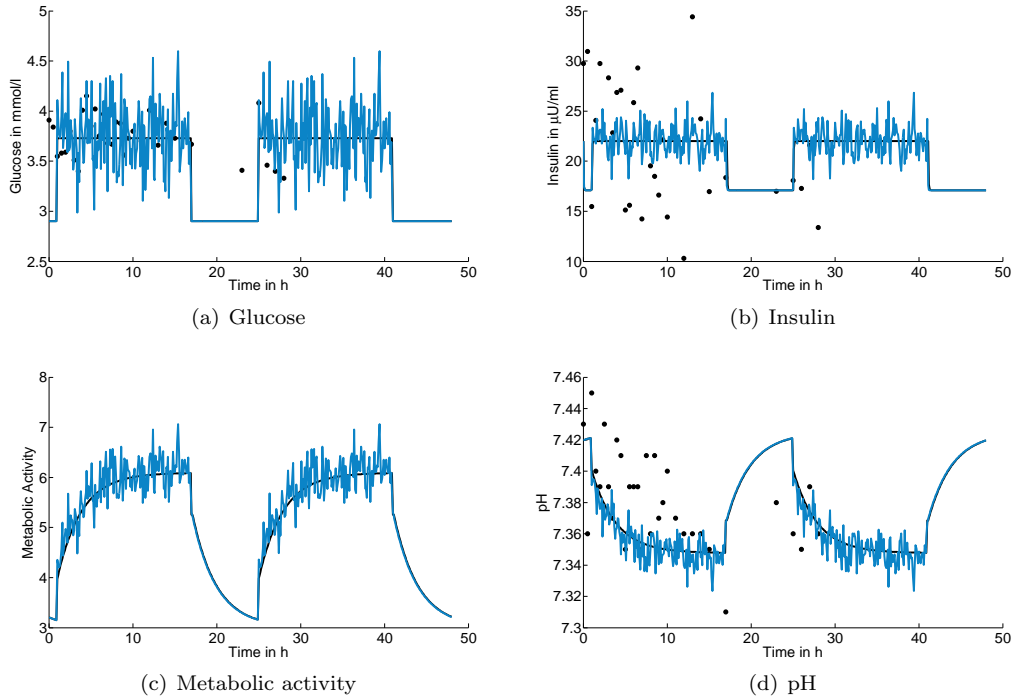


Figure 4: Simulation outcome for metabolic components

3.1.3 Potassium Homeostasis

In Figure 5 we show the simulation outcome for intra- and extracellular potassium as well as the basic characteristics of experimental data. As previously reported by Christinaz et al. [2] we were confronted with a high interindividual variability in the experimental data for intracellular potassium. To overcome this difficulty we introduced cow-specific parameters. Nevertheless, during parameter estimation it turned out to be complicated also for general parameters to find a setting that fits the data for all six study cows simultaneously.

Simulation outcomes for the tissue storage mechanism (K_{TISS}) and saliva (K_{SAL}) represent the actual potassium content in these components (Figure 6).

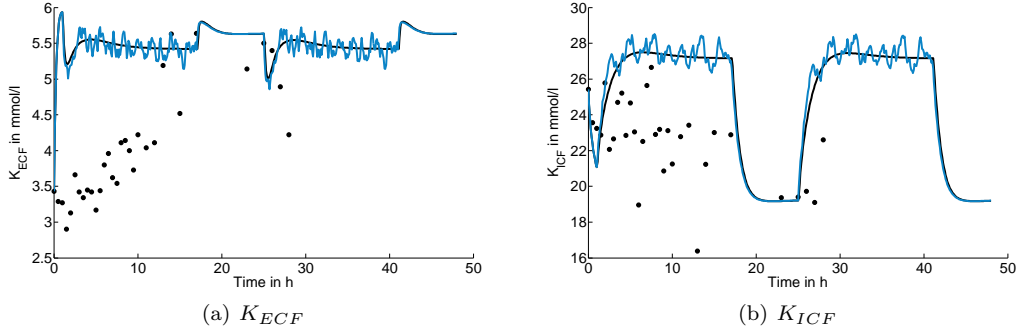


Figure 5: Simulation outcome for intra- and extracellular potassium distribution

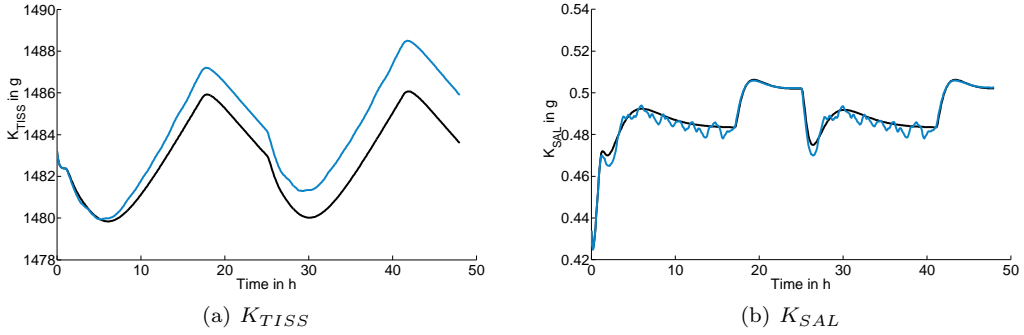


Figure 6: Simulation outcome of recycling and storage mechanisms

3.1.4 Potassium Excretion

The main part of potassium is excreted via K_{URIN} (Figure 7(a)). In the simulation outcome and in the experimental data potassium is accumulated over time. In our model the component K_{URIN} depends on uptake and extracellular content. The very complex renal mechanisms are modeled at a high abstraction level. In Figure 7(b) we observe total potassium excreted in the model which is the sum of potassium excreted via urine, feces and sudor. In the lactating cow remarkable amounts are also excreted with the milk, which is not included in our model yet, as experimental data was taken in non lactating dairy cows.

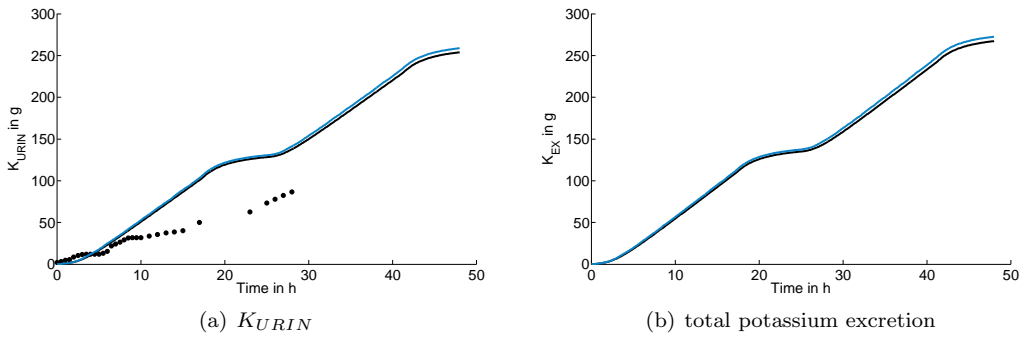


Figure 7: Simulation outcome for potassium excretion

3.2 Simulating Feeding Experiments

3.2.1 Oral Potassium Administration

One of the experiments performed at the Clinic for Ruminants, FU Berlin was the oral administration of potassium. We simulated this experiment and present the results in the following. At 8:00 am the study cows were given 40 g of KCL, which contains 20.7 g potassium. In Figure 8(a) we observe this in our simulation as a peak in K_{FEED} . Experimental data included in the simulation output in Figure 8(b) and 8(c) are from cow A, the same we presented in the previous section. In comparison to the simulation outcomes without intervention (dashed lines) we observe slight differences: K_{ECF} and K_{ICF} stay down after bolus administration, mainly due to higher excretion (Figure 8(d)) via urine. The simulation outcome of the model fulfills the expectations of the systems mechanistic behaviour as described in literature. In potassium replete cows, which the model represents at the beginning of administration, high intake of potassium leads to higher excretion. Main action for increasing excretion is performed by feedforward regulation, i.e. if potassium in K_{GIT} increases, K_{URIN} will increase. If potassium in feed exceeds the limit of resorption, potassium excretion in feces also increases [7].

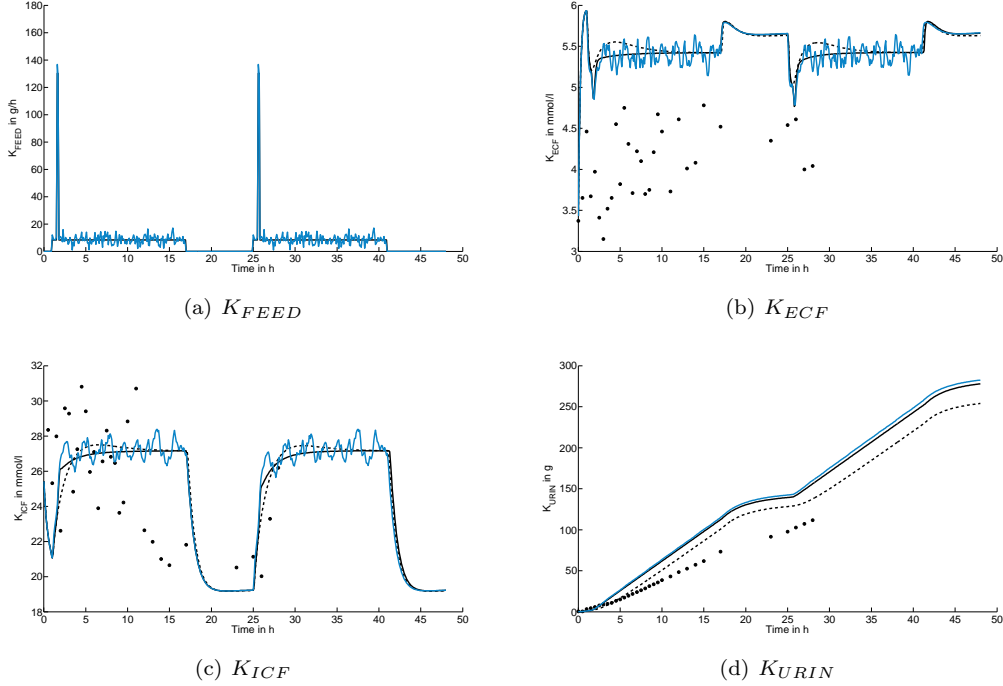


Figure 8: Simulation outcome for oral potassium administration, 20.7 gram, 8:00 am.

3.2.2 Varying Potassium Intake

To validate the mechanisms of the model we varied the oral potassium input in quantity. There was no experimental data available for this approach. The input component K_{FEED} was modified in 4 steps: 0.1 g/h, 1 g/h, 8.3 g/h and 16 g/h which leads to a daily potassium supply of 1.6 g/d, 16 g/d, 132.8 g/d and 256 g/d respectively. In figure 9 we can observe that the more potassium is given to the system the higher K_{ECF} , K_{ICF} and K_{URIN} increase without leaving physiological boundaries. K_{ECF} passes for a short time its upper boundary when 16 g/h potassium is fed, but downregulation mainly via aldosterone fast brings it back into physiological values. It is also visible that for a very low potassium supply (0.1 g/h, 1 g/h) the modeled cow is slowly drifting into hypokalemia, as K_{ECF} , K_{ICF} and K_{TISS} are decreasing.

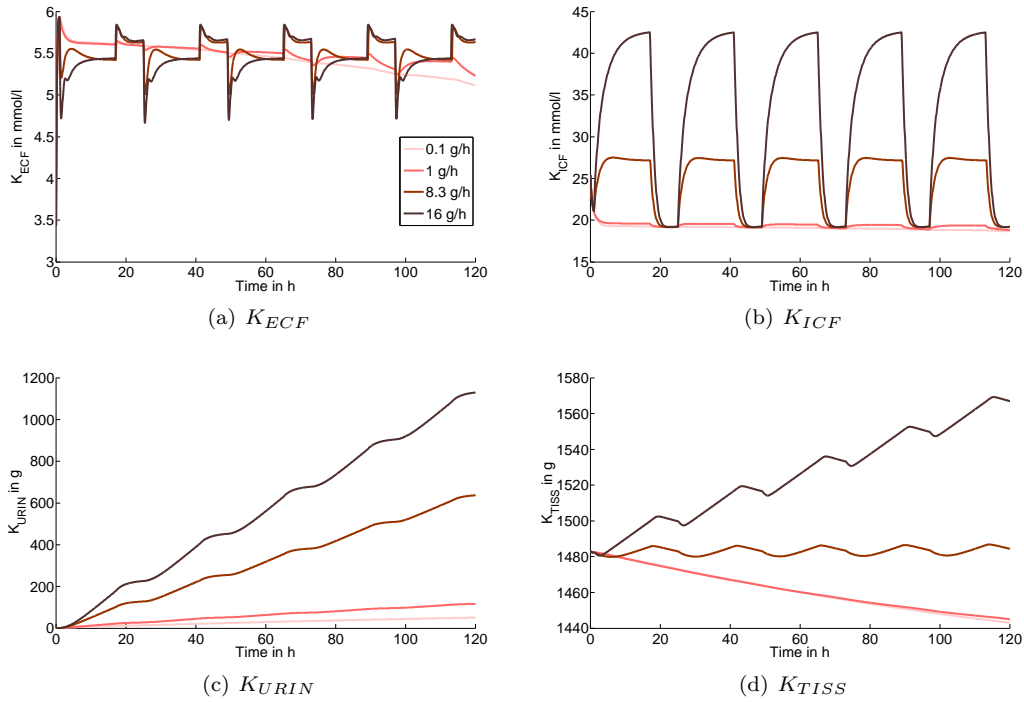


Figure 9: Simulation outcome for oral potassium supply variation with 0.1 g/h, 1.0 g/h, 8.3 g/h and 16.0 g/h.

3.2.3 Feeding Experiments

In another attempt oriented on feeding experiments by Fisher et al. [7] and Pradhan et al. [16] we varied K_{FEED} according to their study design. Fisher et al. [7] studied potassium excess in lactating dairy cows, feeding total mixed ration with 1.6 %, 3.1 % and 4.6 % potassium. Pradhan et al. [16] studied potassium depletion in lactating cows, feeding a diet with 0.15 %. The input component K_{FEED} was modified according to the studies with 1.3 g/h, 23 g/h, 46 g/h and 64 g/h, leading to a daily potassium supply of 21 g/d, 368 g/d, 738 g/d and 1028 g/d, respectively. The results are shown in Figure 10. Especially for the medium potassium supply (orange) the model reproduces the measurements notably accurate.

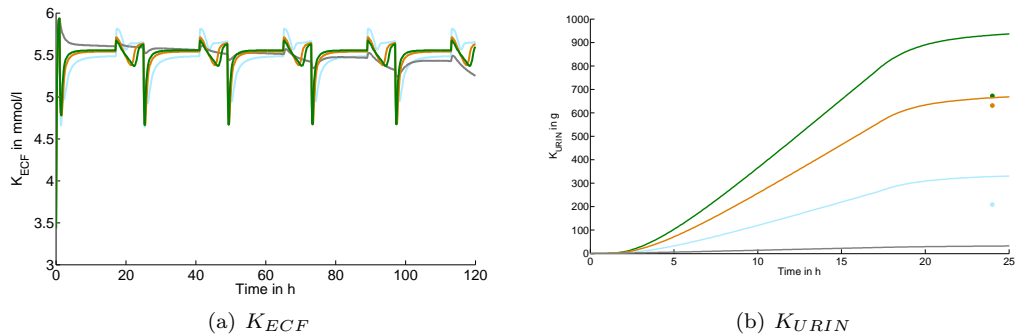


Figure 10: Feed potassium variations of 1.3 g/h (grey), 23 g/h (blue), 46 g/h (orange) and 64 g/h (green) as given from the studies of [7] and [16]. In (b) we compare data points for potassium in urine from the study [7] with simulation curves.

4 Discussion

With our model we are able to simulate dynamics of potassium balance at a whole animal level. The structural design of the model is based on the available experimental data and mechanisms from literature. The motivation to build such a model was an increased interest in hypokalemia in the dairy cow in recent clinical research. Hypokalemia is clinically relevant in postpartum high producing dairy cows. It can be caused by low feed intake, high milk production, hypovolemia, hyperglycemia and metabolic alkalosis [3], corticoid treatment [20] and exo- and endogenous insulin release [9]. A strong correlation between hypokalemia and displaced abomasum has been observed in several studies [3]. Detailed mechanisms are not entirely identified yet and optimal treatment strategies are currently under development. Developing a model for mechanistic relationships of potassium balance in dairy cows is a first holistic approach to gain insight into underlying mechanisms.

When comparing our simulation results with the feeding experiments by Fisher et al. [7] we observe a qualitatively satisfying outcome in the forecast of the excretion of potassium via urine for a given input. Variations can be attributed to individuality of potassium measurements in different studies. Contrary to our model, the cows in Fisher’s study produced milk, which contains remarkable amounts of potassium, and milk production itself influences in the functioning of the entire metabolism.

In the default condition the body weight of the modeled cow is 600 kg with 33 l blood volume. The total potassium in blood tissue, i.e. model components K_{ICF} and K_{ECF} at the initial time is 13.19 g. Therefore the concentration of potassium in blood tissue is 0.46 g/l. Compared to 3 g/kg mean potassium concentration of tissues as found by Bennink et al. [1] the potassium concentration in blood tissue used in our model is very low. Though we show the experimental data from a cow with low potassium erythrocyte content, this can be explained by different potassium concentrations in the different tissues, indicating a low concentration of potassium in blood tissue, much lower than mean. Vogel et al. [25] compared the potassium content of serum and erythrocytes in different mammalian species and found important differences also among species. Their as well as our findings can possibly be traced back to uncertainties in measuring methods, which complicates comparability of studies.

A quantitatively satisfying fit between experimental data and simulation results could not be obtained due to large interindividual variations in the data. Overall, more experimental data for more components involved in potassium balance in more individuals is needed to perform suitable parameter estimation for high and low potassium cows and to extend the model. With a suitable set of data, milk would be a promising approach to fit the model to the individual cow as Ward [26] found potassium milk content to be constant in the individual cow. As hypokalemia mainly occurs in lactating dairy cows, modeling potassium excretion via milk will be indispensable when in a next step we will explore mechanisms for hypokalemia.

The herein presented model and performed experiments are a first attempt to simulate potassium balance in dairy cows. There are still several mechanistic shortcomings, e.g. in renal excretion mechanisms, potassium storage dynamics and mechanisms of hypokalemia, which will be refined with the corresponding experimental data in future.

A Equations

The equations listed below are the full notations of the equations developed in Section 2. Parameters are denoted with p and are numbered according to Table 2.

$$\begin{aligned}
\frac{d}{dt}y_1 &= con \cdot (KgKe - KeKu) - KeKt + KtKe + KiKe - KeKi - KeR - KeKs \\
\frac{d}{dt}y_2 &= (KeKi - KiKe) \cdot con_{vol} \\
\frac{d}{dt}y_3 &= KeKu \\
\frac{d}{dt}y_4 &= KfKg - KgKe + KsKg \\
\frac{d}{dt}y_5 &= \frac{1}{con}(KeKt - KtKe) \\
\frac{d}{dt}y_6 &= \frac{KeKs}{con} - KsKg \\
\frac{d}{dt}y_7 &= KeKu + \frac{KeR}{con} + 0.05 \cdot y_{11} \\
\frac{d}{dt}y_8 &= \left(\frac{p_3}{p_1} \cdot y_{10} - y_8\right) \cdot p_2 \\
y_9 &= 7.5 - \frac{y_{12}}{40} \\
y_{10} &= p_1 + (y_{11} - 8.3) \cdot p_{28} \\
y_{11} &= \begin{cases} 8.3, \text{ continuous option} \\ 8.3 + 3 \cdot \xi, \text{ with } \xi \text{ random variable with standard normal distribution} \end{cases} \\
y_{12} &= 0.1 \cdot y_4 + y_{10}
\end{aligned}$$

B Initial values for ODEs

$$\begin{aligned}
y_1(0) &= p_{11} \\
y_2(0) &= p_{12} \\
y_3(0) &= 0 \\
y_4(0) &= 3.073 \\
y_5(0) &= p_{10} \cdot 0.86 \cdot 2.9 - \frac{1}{con} \cdot \left(\frac{p_{12}}{con_{vol}} + p_{11}\right) \\
y_6(0) &= 0.434 \\
y_7(0) &= 0 \\
y_8(0) &= p_3
\end{aligned}$$

C Rates

$$KfKg = p_{30} \cdot y_{11}$$

$$KgKe = p_{31} \cdot y_4$$

$$KeKs = p_{18} \cdot y_1$$

$$KsKg = p_{32} \cdot y_6$$

$$KeKi = (p_8 + p_9 \cdot H^+(y_8, p_3; 10)) \cdot H^+(y_1, p_{33}; 2) \cdot (1 + p_{21} \cdot H^+(y_9, p_{20}; 10))$$

$$KiKe = (1 + H^-(y_1, p_{29}; 10)) \cdot p_5 \cdot (1 + H^-(y_9, p_{20}; 10)) \cdot H^+(y_2, p_{23}; 2) \cdot (1 + p_{19} \cdot H^+(y_2, p_{14}; 2))$$

$$KtKe = H^-(y_4, p_{15}; 10) \cdot p_{26} \cdot (p_{27} - y_1) \cdot H^+(y_5, 0.99 \cdot y_5(0); 100)$$

$$KeKt = H^+(y_4, p_{15}; 10) \cdot p_{25} \cdot y_1$$

$$KeR = p_4 \cdot y_1$$

$$KeKu = (1 + p_{13} \cdot H^+(y_1, p_{24}; 5)) \cdot p_6 \cdot y_4 \cdot (1 + p_{16} \cdot y_1 \cdot H^+(y_1, p_{22}; 10))$$

D List of Parameters

No.	Value	Unit	Cow specificity	Explanation
p_1	3.73	$\frac{mmol}{l}$	y	Glucose mean value
p_2	28	$\frac{1}{h}$	n	Scaling factor in insulin equation
p_3	22	$\frac{\mu U}{ml}$	y	Insulin mean value
p_4	0.0002	$\frac{1}{h}$	n	Fraction of y_1 per hour leaving via sudor
p_5	14.04	$\frac{mmol/l}{h}$	n	Constant rate K_{ICF} to K_{ECF}
p_6	0.05	$\frac{1}{h}$	n	Scaling factor for influence of K_{GIT} on $KeKu$
p_7	75	-	n	State of random value
p_8	14.91	$\frac{mmol/l}{h}$	n	Constant rate K_{ECF} to K_{ICF}
p_9	9.99	$\frac{mmol/l}{h}$	n	$KeKi$ rate amplification through insulin
p_{10}	600	kg	y	Body weight
p_{11}	3.43	$\frac{mmol}{l}$	y	Initial value K_{ECF}
p_{12}	25.42	$\frac{mmol}{l}$	y	Initial value K_{ICF}
p_{13}	6.01	-	n	$KeKu$ amplification through aldosterone
p_{14}	4	$\frac{mmol}{l}$	n	Threshold for K_{ICF}
p_{15}	22	g	n	Threshold for K_{GIT} influencing $KeKt$ and $KtKe$
p_{16}	3	$\frac{l}{mmol}$	n	Scaling factor for K_{ECF} influencing $KeKu$
p_{17}	0.309	-	y	Hematocrit
p_{18}	0.08	$\frac{1}{h}$	n	Fraction of K_{ECF} transported to K_{SAL}
p_{19}	0.1373	-	n	$KiKe$ amplification through high K_{ICF} levels
p_{20}	7.38	-	y	PH mean value
p_{21}	0.1085	-	n	PH dependent increase of $KeKi$ rate
p_{22}	8	$\frac{mmol}{l}$	n	Threshold for K_{ECF}
p_{23}	15	-	n	Threshold for K_{ICF}
p_{24}	5	$\frac{mmol}{l}$	n	Threshold for K_{ECF}
p_{25}	0.2898	$\frac{1}{h}$	n	Fraction of K_{ECF} moved to K_{TISS}
p_{26}	2.15	$\frac{1}{h}$	n	Scaling factor for $KtKe$
p_{27}	5.95	$\frac{mmol}{l}$	n	Threshold for K_{ECF}
p_{28}	3	$\frac{mmol/l}{g}$	n	Scaling factor K_{FEED} to Glucose
p_{29}	3	$\frac{mmol}{l}$	n	Threshold for K_{ECF}
p_{30}	0.95	-	n	Fraction of K_{FEED} transported to K_{GIT} per hour
p_{31}	0.35	$\frac{1}{h}$	n	Fraction of K_{GIT} transported to K_{ECF} per hour
p_{32}	0.8	$\frac{1}{h}$	n	Fraction of K_{SAL} transported to K_{GIT} per hour
p_{33}	2	$\frac{mmol}{l}$	n	Threshold for K_{ECF}

Table 2: Parameter values.

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