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 being potassium, is indispensable for the prevention of imbalances. Potassium balance in cows is the result of potassium intake, distribution in the organism, and excretion, and it is closely related to glucose and electrolyte metabolism. In this paper, we present a dynamical model for potassium balance in lactating and nonlactating dairy cows based on ordinary differential equations. Parameter values were obtained from clinical trial data and from the literature. To verify the consistency of the model, we present simulation outcomes for 3 different scenarios: potassium balance in (1) nonlactating cows with varying feed intake, (2) nonlactating cows with varying potassium fraction in the diet, and (3) lactating cows with varying milk production levels. The results give insights into the short- and long-term potassium metabolism, providing an important step toward 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 (NRC, 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); however, with an intracellular potassium concentration between 7 and 70 mmol/L in erythrocytes (Christinaz and Schatzmann, 1972), minor damage 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; Mokhber Dezfouli 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 and corticosteroids, both of which 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 shifts from intracellular fluid (**ICF**) to extracellular fluid (**ECF**) and vice versa for alkalosis (Adrogué and Madias, 1981). Clinical relevance and application is reviewed in Russell and Roussel (2007) and Palmer and Clegg (2016).

Received December 12, 2016.

Accepted August 14, 2017.

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Studying veterinary and mathematical viewpoints, we developed a quantitative, dynamic model for potassium balance in dairy cows. We focused on the whole organism instead of narrowing to the cellular level, with an emphasis on metabolic flows between components (e.g., gastrointestinal tract, milk). We compared the outcome of the model simulations with experimental data in a qualitative manner, as the interindividual variability was too large to reproduce the data exactly.

To our knowledge, no published work has presented a biomathematical model of potassium balance in dairy cows or in another livestock species. Mathematical modeling of the involved mechanisms generates quantitative knowledge of the underlying biological processes enabling predictions about the intake and outputs and 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 Database (www.ebi.ac.uk/biomodels-main/) where it can be used by the scientific community and industry to support ration calculation as well as herd and individual cow management.

MATERIALS AND METHODS

Model Description

The modeling objective was to obtain a system of ordinary differential equations (ODE) and algebraic equations, which are 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):

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

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

where $S \geq 0$ denotes the influencing substance, $T \geq 0$ the threshold, and $n \geq 1$ the Hill coefficient. A Hill function is a sigmoidal function between 0 and 1 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 ODE, 4 algebraic equations, and 63 parameters. All simulations were conducted in the software Celldesigner (Ver. 4.4; Systems Biology Institute, Tokyo, Japan) 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.

Experimental Data

In the Clinic for Ruminants of Freie Universität Berlin, a clinical study was conducted to study potassium balance in 6 nonlactating dairy cows. Experimental data from the current study were available for parameter estimation, which was performed with the algorithms NLSCON (Deuflhard, 2004) and simulated annealing (Kirkpatrick et al., 1983). In the data set from the clinical study, we noticed strong interindividual variations between the 6 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 advanced model was based on this data set in a quantitative way, as well as on values from literature. Finally, we obtained a deterministic model that reproduced 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 convert between those. The in- and output components potassium taken up with diet (K_{FEED} ; Table 1) and potassium excreted with urine (K_{URIN} ; Table 1) are specified in gram per hour and gram (accumulated), respectively. The amount of potassium taken up from K_{FEED} is dissolved in the noncellular compartment of the cow blood, potassium in the extracellular blood fluid (K_{ECF} ; Table 1).

For the conversion of mass to concentration, we required the volume in which the substances were dissolved. Blood volume calculation was made on the base of 55 mL of blood/kg of BW, as reported by Reynolds (1953). The BW was set to 600 kg in the default condition. The intra- and extracellular volume of blood

Component	Explanation	Initial value	Unit
DMI	DMI	487.5	g/h
K_{FEED}	Potassium uptake with the diet	5.5429	g/h
K_{ECF}	Potassium in the extracellular blood fluid	0.1751	g/L
K_{ICF}	Potassium in the intracellular blood fluid	0.8973	g/L
K_{URIN}	Potassium excreted with urine, accumulated	0	g
K_{GIT}	Potassium in the gastrointestinal tract	43.1366	g
K_{TISS}	Potassium in tissues except blood and bone	1,509.6	g
K_{SAL}	Potassium in saliva	4.5382	g
K_{MILK}	Potassium in milk, accumulated	0	g
Insulin	Insulin in blood	21.8533	$\mu\text{U/mL}$
$\text{Gluc}_{\text{FEED}}$	Uptake of glucogenic substances with feed	41.6325	g/h
$\text{Gluc}_{\text{PROD}}$	Internal pool of produced glucose	34.03	g
Gluc_{B}	Glucose in blood	0.5466	g/L
$\text{Gluc}_{\text{STOR}}$	Stored glucose in the tissues	3,647.7	g
Metabolic activity	Virtual compound	6.2489	—
pH	pH of blood	7.3438	—

Table 2. Parameters and units (3 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 $\text{Gluc}_{\text{FEED}}^1$ in the rate GsGb^2
p_2	1,600.0	g	Hill threshold for K_{TISS}^1
p_3	22.0	$\mu\text{U/mL}$	Hill threshold for insulin
p_4	0.0001783	L/h	Clearance factor for K_{ECF}^1
p_5	0.563	g/h	Basic rate of potassium in KiKe^2
p_6	0.051	1/h	Scaling factor for the rate KeKu^2
p_7	0.925	g/L	Threshold for glucose in the rate GsGb^2
p_8	0.5994	g/h	Basic rate of potassium in KeKi^2
p_9	0.4016	g/h	Scaling factor for Hill function in the rate KeKi^2
p_{10}	1,400.0	g	Subtrahend for better functioning of the Hill function for K_{TISS}^1 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^2
p_{13}	6.08	—	Scaling factor for Hill function in the rate KeKu^2
p_{14}	0.15639932	g/L	Hill threshold for K_{ICF}^1
p_{15}	32.0	g	Hill threshold for K_{GIT}^1
p_{16}	10.0	—	Scaling factor for Hill function in the rate KeKu^2
p_{17}	16.0	L/h	Basic rate of glucose in the rate GsGb^2
p_{18}	0.0223	L/g	Basic rate of potassium in the rate KeKs^2
p_{19}	0.1373	—	Scaling factor for Hill function in the rate KiKe^2
p_{20}	7.38	—	Hill threshold for pH
p_{21}	0.1085	—	Scaling factor for Hill function in the rate KeKi^2
p_{22}	0.25	g/L	Hill threshold for K_{ECF}^1
p_{23}	0.58649745	g/L	Hill threshold for K_{ICF}^1
p_{24}	0.1962811466	g/L	Hill threshold for K_{ECF}^1
p_{25}	6.6085	L/h	Scaling factor for the rate KeKt^2
p_{26}	49.0279	L/h	Scaling factor for the rate KtKe^2
p_{27}	0.232634885	g/L	Threshold for K_{ECF}^1
p_{28}	25.0	L/h	Fraction of Gluc_B^1 for body use
p_{29}	0.11729949	g/L	Hill threshold for K_{ECF}^1
p_{30}	0.95	—	Fraction of K_{FEED} passing to K_{GIT}^1
p_{31}	0.353	1/h	Fraction of K_{GIT} absorbed to K_{ECF}^1
p_{32}	1.31	1/h	Fraction of K_{SAL} passing to K_{GIT}^1
p_{33}	0.07819966	g/L	Hill threshold for K_{ECF}^1
p_{35}	100.0	g	Hill threshold for $\text{Gluc}_{\text{STORE}}^1$
p_{36}	1.0	L/h	Hill threshold for milk production
p_{38}	1,509.6	g	Hill threshold for K_{TISS}^1
p_{39}	30.0	1/h	Basic rate of glucose in the rate GpGb^2
p_{40}	0.01	g/L	Hill threshold for K_{ECF}^1
p_{41}	20.0	L/h	Factor for insulin clearance
p_{42}	4.5	1/h	Factor for DMI-dependent stimulation of metabolic activity
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 $\text{Gluc}_{\text{FEED}}^1$ to Gluc_B^1
p_{49}	800.0	$\mu\text{U}/\text{mg} \cdot \text{L}/\text{h}$	Scaling factor for Gluc_B^1 influencing insulin production
p_{50}	0.4	g/L	Hill threshold for Gluc_B^1
p_{51}	0.1	1/h	Basic rate of glucose in the rate GpGs^2
p_{52}	1.4	g/L	Scaling factor for the rate KeKm^2
p_{53}	0.01	L/g	Scaling factor for K_{ECF}^1 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}	3,800.0	g	Hill threshold for $\text{Gluc}_{\text{STORE}}^1$
p_{58}	0.01	g/L	Hill threshold for Gluc_B^1
p_{59}	1.0	1/h	Fraction of $\text{Gluc}_{\text{PROD}}^1$ for body use
p_{60}	2.0	g/h	Basic rate of glucose in the rate GsGp^2
p_{61}	5.0	g/h	Hill threshold for $\text{Gluc}_{\text{FEED}}^1$
p_{62}	1.0	L/h	Hill threshold for milk production
p_{63}	800.0	g/h	Increasing factor for the rate GsGb^2 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^1
p_{66}	1.4	h/L	Scaling factor for reduction of glucose body use during milk production

¹As defined in Table 1.²Rates in the model illustrated in Figure 1.

tissue were calculated with the mean hematocrit from the experimental data, which represents the volume of the cellular components in the blood.

The model contains 2 compartments: the extracellular and the intracellular fluid of the blood. The components K_{ECF} , glucose in blood ($Gluc_B$; Table 1), and insulin in blood (Table 1) are located in the extracellular compartment, which has a volume of 22.8 L. The intracellular compartment includes only the component potassium in the intracellular blood fluid (K_{ICF} ; Table 1) and has a volume of 10.2 L. The absolute blood volume of the modeled cow was, therefore, 33 L. The calculations that led 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 that are not yet completely understood. The default condition of the present model was based on the experimental data set 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 .

Potassium Uptake

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

$$y_{DMI} = p_{54} \times 487.5 \times \left[1 - \sin\left(\frac{\pi \times t}{12}\right) \right],$$

where t is time. Integrating y_{DMI} over 24 h, we obtained a daily intake for DMI of $24 \times y_{DMI}(0)$. The study protocol provides an intake of 11,700 g of DMI per 24 h. With $y_{DMI}(0) = 487.5$ g/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/d, 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 for K_{FEED} ,

$$y_{K_{FEED}} = p_{56} \times y_{DMI}.$$

Potassium Absorption. Mechanisms of potassium absorption differ in details among the different segments of the gastrointestinal tract (GIT); hence, we pooled this whole system in 1 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 $KfKg$,

$$KfKg = p_{30} \times y_{K_{FEED}}.$$

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

$$KgKe = p_{31} \times y_{K_{GIT}}.$$

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

$$KsKg = p_{32} \times y_{K_{SAL}}.$$

Thus, for 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 modeled 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 erythrocytes, among 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,

common pharmaceutical interventions are available for the glucose metabolism, such as application of glucocorticoids, whose effects on potassium balance have not been studied.

Glucose metabolism in ruminants is different compared with 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. The resulting intermediary product is pyruvate, which is converted 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 as precursor substances for gluconeogenesis, among other functions.

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 be resorbed as glucose. The fraction of glucogenic substances and resorbable glucose from DMI is pooled (**Gluc_{FEED}**). The **Gluc_{FEED}** 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} as

$$y_{\text{Gluc}_{\text{FEED}}} = p_{46} \times y_{\text{DMI}}.$$

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 (**Gluc_{PROD}**). In this component, we pooled the endogenous production of glucose in the organism as

$$\text{GfGp} = (1 - p_{48}) \times y_{\text{Gluc}_{\text{FEED}}}.$$

The remaining part of **Gluc_{FEED}** goes to the component **Gluc_B**, representing blood glucose, with the rate **GfGb**. This rate represents direct glucose absorption from the intestine, including bypass starch, as

$$\text{GfGb} = 1 - p_{48} \times y_{\text{Gluc}_{\text{FEED}}}.$$

Glucose is taken out of the storage for gluconeogenesis to the **Gluc_{PROD}** component with the rate **GsGp**. This rate is reduced in the case of high **Gluc_{FEED}** levels, modeled with a Hill function, to guarantee the path-

way of **GfGp** to be preferred when high amounts of glucogenic substances in feed are available. If stored glucose (**Gluc_{STOR}**) becomes low, a Hill function (**H**) deactivates the rate as

$$\begin{aligned} \text{GsGp} &= p_{60} \times \text{H}^{-}(y_{\text{Gluc}_{\text{FEED}}}, p_{61}, 5) \\ &\times \text{H}^{+}(y_{\text{Gluc}_{\text{STOR}}}, p_{35}, 10). \end{aligned}$$

Glucose produced in **Gluc_{PROD}** is transported to **Gluc_B** with the rate **GpGb**, except in the case of too high blood glucose levels, when a Hill function switches off the rate as

$$\text{GpGb} = p_{39} \times y_{\text{Gluc}_{\text{PROD}}} \times \text{H}^{-}(y_{\text{Gluc}_{\text{B}}}, p_{50}, 10).$$

The excess of produced glucose is going back to **Gluc_{STOR}** 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 as

$$\begin{aligned} \text{GpGs} &= p_{51} \times y_{\text{Gluc}_{\text{PROD}}} \times \text{H}^{-}(y_{\text{Gluc}_{\text{STOR}}}, p_{57}, 10) \\ &\times \text{H}^{-}(p_{55}, p_{62}, 10). \end{aligned}$$

Thus, for **Gluc_{PROD}**,

$$\frac{d}{dt} y_{\text{Gluc}_{\text{PROD}}} = \text{GfGp} - \text{GpGb} - \text{GpGs} + \text{GsGp}.$$

In vivo, glucose is stored as glycogen. The component **Gluc_{STOR}** represents the pooled glucose storage of an individual. We considered muscle, liver, and kidney as the main tissues storing glucose, and calculated the mass of them with around 280 kg, where 9 kg is liver weight (Pfuhl et al., 2007) for a cow with 600 kg of BW as 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 assumed a maximum storage capacity, which cannot be exceeded, not even with increasing carbohydrate uptake. We calculated the dimension of this storage with 2% glycogen weight in the muscle tissue and 10% in liver (Berg et al., 2002). Thus, a 9-kg liver can store 900 g of glycogen, and about 5,300 g can be stored in muscle with a weight of 265 kg. Finally, we obtained a maximum storage capacity of 6,200 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 $p_7 - y_{\text{Gluc}_B}$. The second part of the rate is only active if milk production is higher than about 5 L/d ($p_{55} > 0.2$ L/h) and is enhancing the rate to provide Gluc_B with enough glucose for the milk as

$$\begin{aligned} \text{GsGb} = & H^+(y_{\text{Gluc}_{\text{STOR}}}, p_{35}, 10) \times H^-(y_{\text{Gluc}_{\text{FEED}}}, p_1, 10) \\ & \times p_{17} \times (p_7 - y_{\text{Gluc}_B}) + H^+(p_{55}, p_{64}, 10) \\ & \times p_{63} \times H^-(y_{\text{Gluc}_B}, p_{65}, 10). \end{aligned}$$

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, as 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 as

$$\begin{aligned} \text{GbGs} = & H^+(y_{\text{Gluc}_{\text{FEED}}}, p_1, 10) \times p_{12} \times y_{\text{Gluc}_{\text{PROD}}} \\ & \times H^-(y_{\text{Gluc}_{\text{STOR}}}, p_{57}, 10) \times y_{\text{Gluc}_B} \times y_{\text{INS}} \times H^-(p_{55}, p_{36}, 10). \end{aligned}$$

Thus, for Gluc_{STOR},

$$\frac{d}{dt} y_{\text{Gluc}_{\text{STOR}}} = \text{GbGs} - \text{GsGb} + \text{GpGs} - \text{GsGp}.$$

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 1 L 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):

$$\begin{aligned} \text{SnkGb} = & H^+(y_{\text{Gluc}_B}, p_{58}, 10) \\ & \times (p_{28} \times y_{\text{Gluc}_B} + p_{59} \times y_{\text{Gluc}_{\text{PROD}}} \times e^{-p_{66} \cdot p_{55}} + p_{55} \times p_{47}). \end{aligned}$$

Thus, for Gluc_B,

$$\frac{d}{dt} (y_{\text{Gluc}_B} \times V_{\text{extra}}) = \text{GfGb} - \text{GbGs} + \text{GsGb} - \text{SnkGb} + \text{GpGb}.$$

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 β cells in response to elevated blood levels of nutrients such as glucose or AA; glucose sensor cells have been found in the pancreas, hypothalamus, and gut (Schuit et al., 2001).

Insulin 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). Thus, for insulin,

$$\frac{d}{dt} (y_{\text{INS}} \times V_{\text{extra}}) = p_{49} \times y_{\text{Gluc}_B} - p_{41} \times y_{\text{INS}}.$$

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. Dry matter intake stimulates metabolic activity with the rate DmMa, which has a base value and declines when DMI is under a certain threshold. The sink term $p_{44} \times y_{\text{MA}}$ guarantees that metabolic activity represents the recent feed intake and does not accumulate:

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

Thus, for metabolic activity,

$$\frac{d}{dt} y_{\text{MA}} = \text{DmMa} - p_{44} \times y_{\text{MA}}.$$

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, calculated as

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

Potassium Homeostasis

Potassium homeostasis in the cow is characterized by a consistent flow of potassium cations between different compartments and tissues; in the model this is

represented by the components K_{ICF} , K_{ECF} , potassium in tissue (K_{TISS}), and potassium in saliva (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 (Türk 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 sweat, 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 $KeKs$ as

$$KeKs = p_{18} \times y_{ECF} \times y_{DMI}.$$

Depending on diet, cows produce up to 138 to 179 L of saliva per day (Van't Klooster et al., 1969), with an individually varying content of potassium between 0.16 to 2.94 g/L (Bailey, 1961; Ward, 1966). 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), and calculated as

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

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 et al., 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} (Svensen, 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} , calculated as

$$KeKi = \left[p_8 + p_9 \times H^+ (y_{INS}, p_3, 8) \right] \times H^+ (y_{K_{ECF}}, p_{33}, 2) \times \left[1 + p_{21} \times H^+ (y_{pH}, p_{20}, 10) \right].$$

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} (Simmons and Avedon, 1959). If K_{ECF} drops un-

der p_{29} , up to 100% more of potassium drifts from K_{ICF} to K_{ECF} (Greenlee et al., 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} , calculated as

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

Thus, for K_{ECF} ,

$$\begin{aligned} \frac{d}{dt} (y_{K_{ECF}} \times V_{extra}) &= KgKe - KeKu - KeKt + KtKe \\ &+ KiKe - KeR - KeKs - KeMi, \end{aligned}$$

and for K_{ICF} ,

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

Tissue Storage. The K_{TISS} represents the potassium content in all tissues except blood and bone tissue. The initial value of K_{TISS} depends on BW. Bennink et al. (1968) studied the potassium content of different tissues in cattle and found mean potassium content of 3 g/kg of BW, which we used to calculate the initial value for K_{TISS} , representing the reservoir of potassium at the beginning of the simulation. The 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 assumed 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, calculated as

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

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

The $KtKe$ is intended to increase if K_{ECF} decreases, so the current rate $KtKe$ is a multiple of $p_{27} - K_{ECF}$. 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, calculated as

$$\begin{aligned} \text{KtKe} = & H^-(y_{\text{K}_{\text{GIT}}}, p_{15}, 10) \times p_{26} \times (p_{27} - y_{\text{K}_{\text{ECF}}}) \\ & \times H^+(y_{\text{K}_{\text{TISS}}} - p_{10}, 0.99 \times p_{38} - p_{10}, 10). \end{aligned}$$

Thus, for K_{TISS},

$$\frac{d}{dt} y_{\text{K}_{\text{TISS}}} = \text{KeKt} - \text{KtKe}.$$

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

$$\text{KeR} = p_4 \times y_{\text{K}_{\text{ECF}}}.$$

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} .

Strong evidence exists 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). Three supposed mechanisms have been observed 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). Our 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, $\text{K}_{\text{ECF}} > p_{22} = 0.25$ g/L, modeled again by a Hill function for K_{URIN} as

$$\frac{d}{dt} y_{\text{K}_{\text{URIN}}} = \text{KeKu}.$$

Thus,

$$\begin{aligned} \text{KeKu} = & \left[1 + p_{13} \times H^+(y_{\text{K}_{\text{ECF}}}, p_{24}, 5) \right] \times p_6 \times y_{\text{K}_{\text{GIT}}} \\ & \times \left[1 + p_{16} \times H^+(y_{\text{K}_{\text{ECF}}}, p_{22}, 10) \right] + p_{53} \times y_{\text{K}_{\text{ECF}}}. \end{aligned}$$

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 liters per hour. Potassium content in milk is constant with $p_{52} = 1.4$ 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

$$\text{KeKm} = p_{55} \times p_{52} \times H^+(y_{\text{K}_{\text{ECF}}}, p_{40}, 10).$$

Thus, for K_{MILK},

$$\frac{d}{dt} y_{\text{K}_{\text{MILK}}} = \text{KeKm}.$$

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

$$\text{GbMi} = p_{55} \times p_{47} \times H^+(y_{\text{Gluc}_B}, p_{58}, 10).$$

As 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 were validated with numerical experiments and clinical data. We have used several conditions (e.g., BW 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 interindividual variability. [See Plöntzke et al. (2013) for our preliminary modeling approach including plots of the data.] Within the experimental data, large inter- and intraindividual variability exists. In particular, the values for K_{ICF}, the measured potassium content in erythrocytes, and insulin showed 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 millimoles per liter; the unit of K_{ECF} and K_{ICF} presented in the plots is millimoles per liter as well. For calculations, the model uses grams per liter.

Figure 2. Simulation outcome for all model components in the default condition. (a) K in DMI (K_{FEED}), glucose in DMI ($Gluc_{FEED}$), and DMI; (b) K in gastrointestinal tract (K_{GIT}), K in intracellular blood fluid (K_{ICF}), metabolic activity (virtual component), and insulin (in blood; Ins_B); (c) K in urine (K_{URIN}), stored K in tissues (K_{TISS}), stored glucose ($Gluc_{STOR}$), and internal pool of produced glucose ($Gluc_{PROD}$); and (d) K in saliva (K_{SAL}), K in extracellular blood fluid (K_{ECF}), glucose in blood ($Gluc_B$), and pH.

In the section Default Condition, we first present outcomes from the simulation of potassium balance without intervention in a nonlactating cow. To verify the consistency of the model, 3 experiments were performed. In experiment 1, the DMI was varied; in experiment 2, the potassium fraction in the diet K_{FEED} was varied; and in experiment 3, simulation outcomes for a lactating cow are shown.

Default Condition

The default condition of this model was based on the experimental data that were used to build the

preliminary model (Plöntzke et al., 2013; see Material and Methods). The study data were collected from 6 nonlactating dairy cows fed 11.7 kg of DMI per day (Figure 2a) containing 1.137% of potassium, which can be observed in the simulation of the component K_{FEED} (Figure 2a), leading to 133 g of potassium uptake per day.

The component K_{GIT} (Figure 2b) pools the amount of potassium absorbed in the gastrointestinal tract. One can see the potassium ingested with K_{FEED} , minus 5%, which are obligatorily excreted with the feces, plus the potassium from saliva, K_{SAL} (Figure 2d), which is swallowed and absorbed to K_{GIT} .

Potassium from K_{GIT} is passed to K_{ECF} , the extracellular fluid of the cow blood. From there, potassium is moved to the intracellular fluid K_{ICF} (Figure 2b), excreted with urine K_{URIN} (Figure 2c) and sweat, 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 and 2.9 g/L in cows.

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

In the study of Christinaz and Schatzmann (1972), cows were found to have erythrocyte potassium concentrations, corresponding to the model component K_{ICF} , between 7 and 70 mmol/L. In our study, most individuals were found to have an erythrocyte potassium concentration of around either 20 or 50 mmol/L, based on genetic variation with no breed influence (Christinaz and Schatzmann, 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} (Figure 2c) with K_{ECF} , a cow loses 27.9 g potassium during the 10 d simulation period. In Figure 2c, one can observe the accumulated excretion of potassium with K_{URIN} . Within the 10-d simulation period, the cow excreted an average of 130.6 g of potassium per day, which exceeds the ingested amount of 126.3 g per day by 4.3 g. This potassium loss was fed mainly from K_{TISS} .

The $Gluc_{FEED}$ (Figure 2a) was 8.5% of DMI in the default condition, representing carbohydrates convertible to glucose. Its dynamic follows the dynamic of DMI. In $Gluc_{PROD}$ (Figure 2c), glucogenic substances are converted to glucose and nourish blood glucose ($Gluc_B$; Figure 2d) and are stored in $Gluc_{STOR}$ (Figure 2c), whereby the loss in the 10-d simulation period was 4.6 g, representing a relatively balanced nutrition. Due to the model construction, pH was very stable even when the input was varied within maximal physiologi-

Figure 3. Potassium in extracellular blood fluid (K_{ECF}), K in intracellular blood fluid (K_{ICF}), insulin in blood (INS_B), glucose in blood ($Gluc_B$), and DMI with a vertical logarithmic scale to enable the direct comparison between the species developing over time. Note that the curve for DMI is interrupted, because log 0 is not defined.

cal values; that is, pH can be, at most, 7.43 if metabolic activity is zero, and minimum values will not fall below $\text{pH} = 7.34$ if DMI is above 40 kg. In Figure 3 the main components of the system are shown together with a vertical logarithmic scale to enable comparison.

Experiment 1: Variation of DMI

In this experiment, DMI 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} was 0.2, 0.56, 0.92, 1.28, 1.64, and 2.0 g/h, the cow was consuming 2,340, 6,552, 10,764, 14,976, 19,188, and 23,400 g of DMI, respectively. The recommendations by the NRC (2001) describe a maximum feed intake of up to 4% BW, which would be 24 kg of DMI for the cow modeled here.

Figure 4a 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 4b shows the simulation result for the model component K_{TISS} with varied DMI. With increasing DMI, more potassium is stored in the

Figure 4. Dry matter intake is varied via p_{54} , the variation parameter for the default DMI, in steps of 0.36 between 0.2 and 2.0 g/h. When p_{54} was 0.2 g/h (0.56, 0.92, 1.28, 1.64, and 2.0 g/h), the cow was consuming 2,340 g (6,552, 10,764, 14,976, 19,188, and 23,400 g) of DM, respectively. Simulation outcome for the model component K in urine accumulated (K_{URIN} ; a), potassium stored in tissues (K_{TISS} ; b), glucose in blood (Gluc_B ; c), and stored glucose ($\text{Gluc}_{\text{STOR}}$; d) are shown. With increasing DMI potassium excretion with urine increases (a); more potassium is stored in tissues (b), whereas for lower DMI the stored K is consumed; with increasing DMI, we observed increasing values of glucose in blood (c), mainly in the peak values; more glucose is stored in the storage component (d), whereas for lower DMI the stored glucose is consumed.

storage component K_{TISS} due to the fact that the cow is ingesting more potassium than she needs. In Figure 4c, one can observe the simulation outcome for the model component $Gluc_B$ under varying DMI.

The peak blood glucose values increased with increasing DMI, and thus increased glucose intake. Blood glucose values stayed in their physiological range (see section Mechanisms).

In Figure 4d, one can observe the simulation outcome for the model component $Gluc_{STOR}$ for varying DMI. The dynamics of the glucose storage component were 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 decreased while glucose 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 TMR 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. Figure 5 shows data of potassium in urine from the field experiment and model simulations under similar conditions; note that these data were not used for model development or parameter fitting. With additional data (e.g., BW 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} was varied as 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 of milk/d, respectively. Dry matter intake was 200% of the default condition and $Gluc_{FEED}$ was 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 (NRC, 2001).

Figures 6a to h show the simulation outcomes in our experiment. In Figure 6a and b, 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 noticed that, with an increasing demand for potassium, K_{ECF} was getting marginally lower but kept in its physiological range and did not drop into hypokalemic regimens.

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. The K_{ICF} increased due to higher amplitudes in glucose metabolism. Insulin rose and, subsequently, the rate of $KeKi$ (Figure 6c), at which potassium moves from extracellular to intracellular space, increased; this mechanism has been shown for splanchnic tissue and for skeletal muscle cells (DeFronzo et al., 1980).

In the simulation outcome for the $KeKu$ rate (Figure 6d), one can observe the potassium moving from extracellular space to urine in grams per hour. 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 6f, g, and h 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 (Figure 4c). With 20% DMI, the glucose input via $Gluc_{FEED}$ was high enough to meet the demand of higher milk production of 38.4 L/d. This submodel is a solid start to progress dynamic modeling of glucose metabolism for lactating ruminants.

Figure 5. Simulation result (sim) for model components K in urine (K_{URIN}) 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 TMR 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 as Fisher 1 ($p_{54} = 1.97$, $p_{55} = 1.32$, $p_{56} = 0.016$); Fisher 2 ($p_{54} = 2.03$, $p_{55} = 1.31$, $p_{56} = 0.031$); and Fisher 3 ($p_{54} = 1.91$, $p_{55} = 1.24$, $p_{56} = 0.046$).

Figure 6. 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 L/h (0.32, 0.64, 0.96, 1.28, and 1.6 L/h), the cow produces 0 L (7.7, 15.4, 23.0, 30.7, and 38.4 L) of milk per day, respectively. Dry matter intake is 200% of the default condition and $\text{Gluc}_{\text{FEED}}$ is set to 20% of DMI. Simulation outcomes for the model components are shown. With increasing milk production the amplitude of K in extracellular blood fluid (K_{ECF} ; a) increases; the mean values and amplitude of K in intracellular blood fluid (K_{ICF} ; b) increase with increasing milk yield; the amplitude of the rate of K flow from extracellular to intracellular blood fluid (KeKi ; c) increases; and the amplitude of the rate of K flow from extracellular blood fluid to urine (KeKu ; d) decreases and less potassium is excreted with urine. With increasing milk production, less potassium is stored and we observed a decrease of amplitude and values of stored K in tissues (K_{TISS} ; e); glucose in blood (Gluc_B ; f) increases its peak values; the amplitude of the internal pool of produced glucose ($\text{Gluc}_{\text{PROD}}$; g) increases; and stored glucose in tissues ($\text{Gluc}_{\text{STOR}}$; h) decreases. The lower milk production is the more glucose is stored. For higher milk production the storage is consumed.

CONCLUSIONS

We introduced a mathematical model for the potassium balance in lactating and nonlactating dairy cows, including an important submodel for glucose metabolism. The simulation outcomes for the default condition, as well as for 3 different experiments, show a satisfying consistency with literature knowledge. In particular, a comparison of model simulations with data from Fisher

et al. (1994) show that the model can reproduce the trends in these data, although these data were not used during the modeling process. This validates our approach. 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 to model glucocorticoid therapy,

Figure 6 (Continued). 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 L/h (0.32, 0.64, 0.96, 1.28, and 1.6 L/h), the cow produces 0 L (7.7, 15.4, 23.0, 30.7, and 38.4 L) of milk per day, respectively. Dry matter intake is 200% of the default condition and $\text{Gluc}_{\text{FEED}}$ is set to 20% of DMI. Simulation outcomes for the model components are shown. With increasing milk production the amplitude of K in extracellular blood fluid (K_{ECF} ; a) increases; the mean values and amplitude of K in intracellular blood fluid (K_{ICF} ; b) increase with increasing milk yield; the amplitude of the rate of K flow from extracellular to intracellular blood fluid (KeKi ; c) increases; and the amplitude of the rate of K flow from extracellular blood fluid to urine (KeKu ; d) decreases and less potassium is excreted with urine. With increasing milk production, less potassium is stored and we observed a decrease of amplitude and values of stored K in tissues (K_{TISS} ; e); glucose in blood (Gluc_B ; f) increases its peak values; the amplitude of the internal pool of produced glucose ($\text{Gluc}_{\text{PROD}}$; g) increases; and stored glucose in tissues ($\text{Gluc}_{\text{STOR}}$; h) decreases. The lower milk production is the more glucose is stored. For higher milk production the storage is consumed.

a typical veterinarian intervention in cows related to potassium metabolism. In addition, we would like to validate the model with more data.

ACKNOWLEDGMENTS

This work was partially supported by the German Federal Ministry of Education and Research (BMBF, Berlin, Germany). J. Plöntzke and M. Berg gratefully acknowledge funding from e:Bio project BovSys (FK-

Z031A311, Jülich, Germany). We authors thank Alexander Lange (Anhalt University of Applied Sciences, Köthen, Germany) for proofreading the manuscript.

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