SimHerd-Flex application for estimating the cost-benefit of using X-Zelit

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General description

Response Surface Model

A SimHerd-Flex application is a response surface model (RSM) of the full SimHerd model. An RSM describes the behavior of the full SimHerd model as good as possible, while easier and faster to use. In this documentation paper, the method and choices behind the RSM are presented. Figure 1 presents a simplified illustration of how an RSM is created.

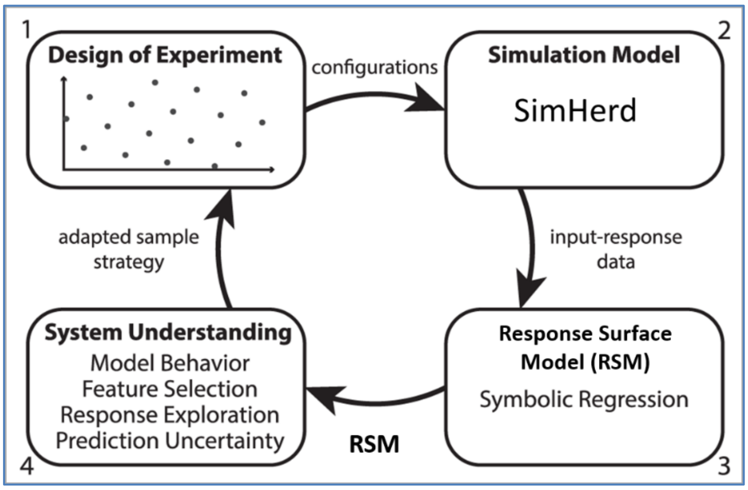

Figure 1: Making a Response Surface Model (RSM) modified after Willem en Stijven (2014)

Design of Experiment

Step 1 in the creation of an RSM (figure 1) is the Design of a simulation experiment to be executed with the full SimHerd model. The design of this study covered a total of 1728 scenarios in which different levels of disease risk were studied. The levels of disease risk were simulated for different levels of herd-level key-performance indicators like milk yield potential and replacement rate but also parameters like milk price and treatment costs. The 1728 scenarios thereby contain information on the value of different disease risk levels, given many combinations of herd-specific settings. The 1728 combinations of herd-specific settings can be interpreted as 1728 different herds.

Simulation model with the full version of the SimHerd model

In step 2 (figure 1) each of the 1728 scenarios were simulated by SimHerd over a period of 10 years. The simulated technical results (like milk yield per cow-year) and economic results (like Gross Margin (GM) per cow-year) of the last 5 simulation years were used in the next step.

RSM or symbolic regression

In step 3, a regression model was built to describe the simulated output parameters as a function of the model's input parameters. In other words, the regression model describes the simulated GM per cow-year (the dependent variable, y) as a function of the input parameters like the herd's disease risk and milk price (the independent variables, x's). This regression model is also referred to as the RSM. In step 4, it was evaluated to what extent the RSM is able to describe the 1728 data points. Furthermore, the behavior of the RSM was studied when using input parameters (x's) beyond the range of original input parameters from the design of experiment (extrapolation). From these evaluations it was concluded that expanding the design of experiment and thereby re-running the RSM cycle (i.e. repeating steps 1 to 4 in Figure 1) was not necessary.

User-interface construction

The RSM is built into a spreadsheet in Microsoft Excel, where input parameters (the x's) are presented to the user as changeable parameters (blue + and – buttons in Figure 2). The output parameters (the y's) of the RSM represent the simulated change in for example milk yield and benefit. Accordingly, the profit is calculated as the benefit reduced by the costs of the intervention. The intervention in this SimHerd-Flex application was the use of X-Zelit at a certain cost per cow per year. The Excel spreadsheet was converted into html and be used on-line.

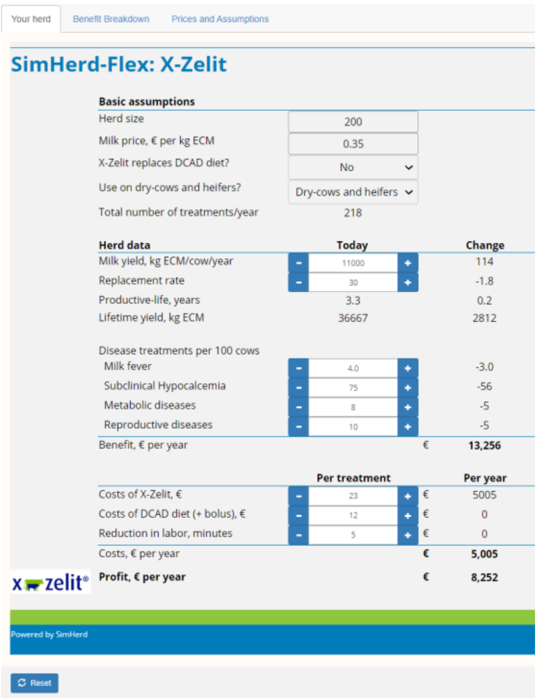

Figure 2: user-interface of the X-Zelit application of SimHerd-Flex

Milk fever and subclinical hypocalcemia in SimHerd

Before creating an RSM (Figure 1), the assumed effects of X-Zelit on disease risk and the assumed effects of diseases on cow-level performance were defined.

Incidence level of milk fever and subclinical hypocalcemia

The default value for the incidence of clinical milk fever and sub-clinical hypocalcemia was 4% and 50%, respectively. These values, like any other value, can be changed on the user-interface. The default values are based on the literature study that has been added to this document as an Appendix.

Effect of X-Zelit and DCAD on reducing hypocalcemia

Based on the literary study that is attached to this document as an Appendix, it was furthermore assumed that X-Zelit reduces the risk of HypoCalcemia by 77%. It was also assumed that clinical milk fever is reduced by 77% as a consequence of X-Zelit.

In the SimHerd-Flex application it is also possible to estimate the impact of using X-Zelit in case no other preventive strategy against HypoCalcemia is in place today. In this situation, the reducing effect is simply 77%, as mentioned above. But is also possible to estimate the effect of replacing a DCAD diet with X-Zelit. This means that the DCAD strategy, and it's reducing effect on hypocalcemia, is removed before it is being replaced by X-Zelit. In this situation it is important to quantify the reducing effect of a DCAD diet. This effect was assumed to be 32% and was also based on the literature study that is added to the Appendix.

In case the SimHerd-Flex application is used to quantify the effect of replacing DCAD with X-Zelit, the net effect in terms of reducing HypoCalcemia is 64% and calculated as follows:

- When assuming today's risk of HypoCalcemia (with a DCAD diet) to be 25%, the risk will be 37% when removing the DCAD diet (=25%/(1-32%), where the 30% is the reducing effect of the DCAD diet).
- Subsequently, when implementing X-Zelit, the risk of HypoCalcemia will be 9% (=37%*(1-77%), where 77% is the reducing effect of X-Zelit).
- The net effect of the replacement is a reduction from 25% to 9%, which is a 64% reduction (=1-(9%/25%)).
- Regardless of today's risk of HypoCalcemia (25% or 5% or 50%) the net effect is a 64% reduction.

The effect of milk fever and hypocalcemia on cow-level performance

As described in the previous paragraph, it is assumed that X-Zelit and a DCAD diet have a reducing effect on milk fever and hypocalcemia. The next step in parameterizing the simulation study, is to quantify the effects of milk fever (MF) and subclinical hypocalcemia (SCH). This is presented in Table 1.

Table 1: assumptions on the cow-level effects of milk fever (MF) and subclinical HypoCalcemia (SCH)

	MF	SCH
Milk yield reduction (of 305-d yield)	1% [a]	0.8% [c]
Mortality risk	13% [b]	0%
Risk factor for other diseases (OR)		
-Dystocia	5 [b]	1
-Retained Placenta	2 [b]	3.4 [d]
-Metritis	1 [b]	3.24 - 4.3 [e]
-Ketosis	3 [b]	5.5 [f]
-LDA	3 [b]	3 - 3.7 [g]
-Mastitis	1.1 [b]	1
Conception rate (OR)	1 [b]	0.27-0.46 [i]

[a] Rajala-Schultz et al. 1999

[b] Østergaard et al. 2003

[c] Bascom, 2016

[d] Rodriguez et al. 2017

[e] Martinez et al., 2012, Rodriguez et al. 2017

[f] Rodriguez et al. 2017

[g] Chapinal et al., 2011, Rodriguez et al. 2017

[i] Caixeta et al., 2017

The risk factors for other diseases that are presented in Table 1, are illustrated in Figure 3. The risk for dystocia is 5 times higher, in case the cow has suffered from a case of milk fever.

All other diseases presented in Figure 5 also have an effect on milk yield, survival and fertility as described for MF and SCH in Table 1. All assumptions for these other diseases are documented in Østergaard et al. 2003 (dystocoa, metritis, ketosis, displaced abomesum) and Østergaard et al. 2005 (mastitis).

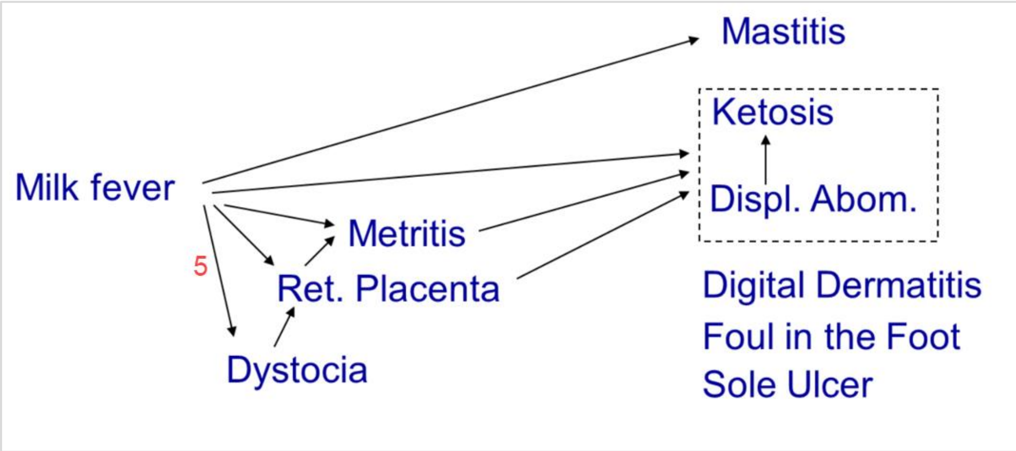

Figure 3: disease interrelationship as assumed in SimHerd.

Design of Experiment

A simulation experiment was designed with the purpose of covering the area of interest as well as possible. For this project, the area of interest concerns the diseases that are affected by the intervention (X-Zelit supplementation) and other parameters of herd management that are important when quantifying the economic value of the disease risks. The diseases that are affected by X-Zelit are presented in Table 1. In the design of experiment, three different levels of milk fever were created since this was the most important disease in this context. For all other parameters two levels were created (Tabel 2).

Other KPI's that are relevant when assessing the economic impact of a disease (by SimHerd) are the herd's milk yield level, replacement rate and reproductive efficiency. Based on experience with the SimHerd model, differences in these KPI's cause differences in the estimated economic value of a disease. In addition to the KPI's, different levels of prices and costs were also created in the experiment (Table 2).

In case of a full experimental design, exploring all possible combinations of all levels, the sum of combinations would have been 49152. This would have resulted in a huge dataset of simulated results. Experience with the model tells us that not all combinations are relevant to study. Instead, all combinations of diseases levels and other KPI's were studied in the experiment (3 levels of milk fever, by 2 levels of subclinical milk fever, …, by 2 levels of reproductive efficiency: 3x2x2x2x2x2x2 = 192 combinations). These 192 combinations were simulated given one standard set of prices. Furthermore, the same 192 combinations were studied 8 times. For each time, one of the eight price-levels was set at the high level, while keeping the other seven prices constant. The 192 combinations were thereby simulated nine times, resulting in a total of 1728 scenarios.

Table 2: the different levels of disease risks, other KPI's and prices and costs that were simulated in the simulation experiment behind the SimHerd-Flex application of X-Zelit.

	Level		
	Low	Med	High
Disease risk			
Milk fever (MF)	1%	5%	13%
Subclinical milk fever (scMF)	6%		68%
Metabolic diseases (MD) [1]	1%		31%
Reproductive diseases (RD) [2]	3%		55%
Other KPI's			
Milk yield potential, kg per 305 days	9000		13000
Culling risk	22%		38%
Reproductive efficiency	15		24
Prices and costs			
Milk price, kr. pr. kg ECM	2,6		3,6
Feed price, kr. pr. kg DM	1,45		2,175
Treatment costs, MF*	1573		2360
Treatment costs, MD* [3]	1573/905		2360/1358
Treatment costs, RD*	816		1224
Insemination costs, kr. pr. breeding	180		270
Sales price heifers, kr. pr. heifer	11000		16500
Slaughter price, kr. pr. cow	6500		9750

[1] Ketosis and displaced abomasum (disease level of ketosis is on average three times higher compared to the disease level of DA, 3:1)

[2] Metritis and retained placenta (1:1)

[3] Displaced Abomasum / Ketosis

* kr. pr. case

In Table 3 the parameterization of six of the 1728 scenarios is presented. These six scenarios enable to estimate three economic values. First of all, to estimate the value of reducing the risk of milk fever given a low level of all the other parameters (scenario 17 versus scenario 1). Secondly, to estimate the value of reducing the risk of milk fever given a high level of other metabolic diseases (MD) in the herd (scenario 18 versus scenario 2). Since milk fever is a risk factor for other metabolic disease (Table 1), milk fever is expected to affect economic performance more in case the herd has many metabolic diseases. Thirdly, to estimate the value of reducing the risk of milk fever given a high milk yield level in the herd (scenario 97 versus scenario 113). It is assumed that milk fever reduces milk yield by a proportion (Table 1), so the absolute amount of milk yield reduction due to milk fever is higher in a herd with a high milk yield level.

Table 3: parameterization of 6 scenarios of the simulation experiment

Scenario	Milk yield level	Replacement rate	Repro efficiency	Milk fever	scMF	MD	RD
1	Low	Low	Low	Low	Low	Low	Low
2	Low	Low	Low	Low	Low	**High**	Low
17	Low	Low	Low	**High**	Low	Low	Low
18	Low	Low	Low	**High**	Low	**High**	Low
97	**High**	Low	Low	Low	Low	Low	Low
113	**High**	Low	Low	**High**	Low	Low	Low

Simulation modelling with SimHerd

SimHerd is a dynamic, stochastic, and mechanistic simulation model of dairy farm including youngstock (Østergaard et al. 2005). Each of the 1728 scenarios were simulated by SimHerd over a period of 10 years. To avoid the influence of the initial herd, only the average results over the last 5 years were studied. The number of replicates used per simulation was 500. In Table 4 the simulated results of the six scenarios from Table 3 are presented.

Table 4: simulated results of six scenarios of the simulation experiment

Scenario	Milk fever per 100 cow-years	Metabolic diseases per 100 cow-years	Replacement rate	Milk yield per cow-year	Gross Margin per cow-year
1	0,8	1,0	26,2	9622	13918
2	0,8	11,0	26,6	9595	13687
17	10,5	1,4	27,3	9583	13554
18	10,3	13,0	27,9	9550	13283
97	0,8	1,3	26,3	12898	20218
113	10,6	1,3	27,3	12841	19827

Response surface model (RSM)

Not only for the six scenarios in Table 3, but for all 1728 combinations of scenarios, prices and costs, the gross margin (GM) was simulated. The goal of making an RSM is to describe these simulated values for GM (the dependent variable, y) as a function of the input parameters (the independent variables, x's, as presented in Table 2).

Creating an RSM that describes GM is done in two steps.

Step 1: describing the technical performance of the herd, like milk yield per cow-year (MlkPrKo; the dependent variable, y) as a function (x's) of the disease levels (like MF, scMF, Repro and Metab) and other herd-level KPI's (InvolCull (culling risk) and InsChance (reproductive efficiency). The model below contains main effects, but also interaction terms between milk yield potential of the cow and milk fever risk (*TopYield:MF).*

MlkPrKo.mean = - 39.9434288 + 222.2479595 * TopYield - 15814.7300983 * InvolCull + 406.7312993 * InsChance + 262.4991776 * MF + 170.3447304 * scMF - 178.7434073 * Repro - 55577.6217045 * Metab - 9.8730778 * TopYield:MF - 5.8427166 * TopYield:scMF - 128809.2305271 * MF:Metab - 530.5029773 * MF:Repro - 274962.5949993 * scMF:Metab - 493.6558771 * scMF:Repro + 4729.4839261 * InvolCull:MF + 906.3470166 * InvolCull:scMF - 456.2701211 * InsChance:MF - 98.4464342 * InsChance:scMF

In step 1, an RSM was not only created for MlkPrKo but also for other technical performance indicators of the herd, like cow mortality (DodKoPKo) and surplus heifers sold (klvkviersolgt).

Step 2: describing the economic performance of the herd (DBprko1=gross margin per cow-year, y's) as a function of the technical performance, like milk-yield per cow-year (MlkPrKo) but also prices and costs like milk-price (KrPrEkm) and feeding costs (KrFeed). In other words, the dependent variables from step 1 are used as independent variables in step 2.

DbPrKo1.mean = - 7197.48501 - 2.93253 * **MlkPrKo.mean** - 109.15883 * DodkoPKo.mean - 28.06900 * klvkviersolgt.mean - 51.81040 * UdskPct.mean + 55.75794 * InsPrKo.mean + 62.93302 * Leveringpct.mean + 2.29263 * MFprko.mean - 0.44302 * scMFprko.mean + 0.15713 * ReproPrKo + 0.37936 * MetabPrKo - 4.38392 * KrPrEkm - 2292.90771 * KrFeed + 0.00211 * KrPrKlKv - 28.83090 * KrPrKgKo - 0.00357 * KrMF - 0.00588 * KrRepro - 0.00728 * KrMetab - 1.16268 * KrNSBT + 0.98891 * **MlkPrKo.mean**:KrPrEkm - 0.45054 * **MlkPrKo.mean**:KrFeed + 0.02993 * **MlkPrKo.mean**:Leveringpct.mean + 0.00492 * klvkviersolgt.mean:KrPrKlKv + 6.08765 * UdskPct.mean:KrPrKgKo - 0.00930 * MFprko.mean:KrMF - 0.00971 * ReproPrKo:KrRepro - 0.00591 * MetabPrKo:KrMetab - 0.78755 * InsPrKo.mean:KrNSBT

User-interface construction

A spreadsheet was built in Excel in which all the above reported information was incorporated. The Excel sheet was accordingly converted into html, which is the application that the user works with.

Strategy choices

The user can specify whether X-Zelit should replace a DCAD diet or not (arrow 1). In case X-Zelit doesn't replace a DCAD diet, a 75% reduction of milk fever and subclinical hypocalcemia is assumed. In case X-Zelit does replace a DCAD diet, a reduction of 64% is assumed. The user can also choose whether X-Zelit is going to be used on dry cows and high-pregnant heifers, or on dry-cows only (arrow 2). This choice affects how many treatments there will be every year (arrow 3) but also the effect of X-Zelit; when only using it on dry-cows, no effect in the first parity will be included in the calculations.

Reduction of the effect of X-Zelit

The assumptions on the effect of X-Zelit on milk fever and subclinical HypoCalcemia were directly incorporated. The user enters a value for these disease in the Today situation, and the resulting change in disease incidence is a direct function of the 75% reduction that was assumed for X-Zelit; 4 cases are of milk fever are reduced by 3 cases, as illustrated by the red square in Figure 4.

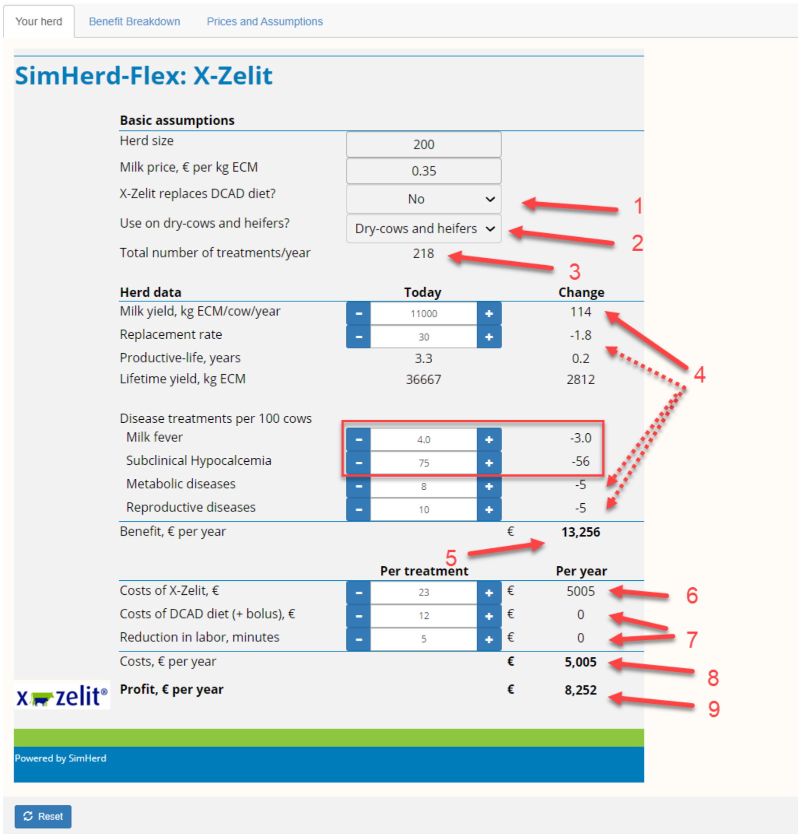

Figure 4: user-interface of the SimHerd-Flex application for X-Zelit

The RSM model for benefit

As described in the previous paragraph, in the first step of constructing an RSM, a first RSM model is created that describes the technical performance of the herd, like milk yield per cow-year. In Figure 4, the result of this first RSM for milk yield per cow-year is presented (solid arrow 4). In the same way, an RSM was created for replacement rate, metabolic diseases and reproductive diseases (dotted arrow 4).

Accordingly, the result of the second RSM, that describes the economic performance of the herd, is presented as the benefit (arrow 5). The independent variables of this RSM are the technical performance like milk-yield per cow-year (+114 kg ECM), disease incidence (-3 cases of milk fever and -5 cases of reproductive diseases) and prices and costs (solid red arrow 3).

The calculation of costs

To predict the change in Gross Margin (or benefit) an RSM model was created, as explained in the previous paragraph. Calculation of the costs is rather straightforward. The costs of X-Zelit per year (arrow 6) are a consequence of the costs per treatment that can be modified by the user and the number of treatments per year (arrow 3). The costs of the DCAD strategy are both the costs of the product that is used and the time that is saved when replacing a DCAD strategy with X-Zelit (arrow 7). The sum of all costs is indicated by arrow 8.

The profit is indicated by arrow 9 and calculated as the benefit minus costs.

Benefit breakdown

The increase in benefit of €13256 is explained in more detail on the sheet "Benefit breakdown". The pie chart on this sheet explains where the increase of benefit comes from. It shows that almost 50% of the increase in benefit comes from the increased sales of milk on the farm and only 17% of the increase in benefit is due to the fact that the farm has fewer disease treatments costs as a consequence of X-Zelit. The "Livestock sales" represents the increase in the sale of pregnant heifers, since fewer cows need to culled.

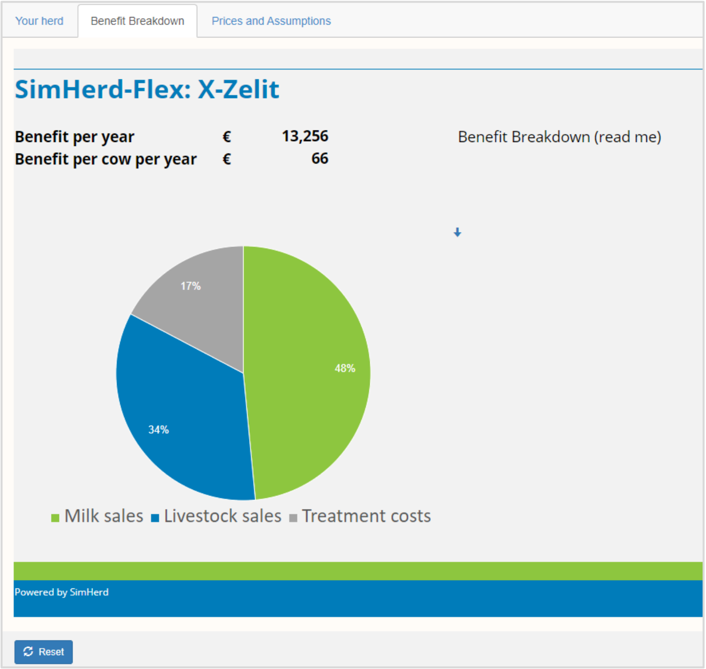

Figure 5:

On the sheet “Prices and assumptions” (Figure 6) all relevant prices but also the efficacy of X-Zelit and DCAD diet can be modified here. Any changes that are made on this sheet are directly incorporated into the application and result in modified estimations of the benefit. The SimHerd-Flex application has been created for different country settings (Denmark (Kr.), Europe (€), Canada, UK, USA). Depending on the country, SimHerd-Flex uses different default assumptions for parameters like yield level but also prices and costs.

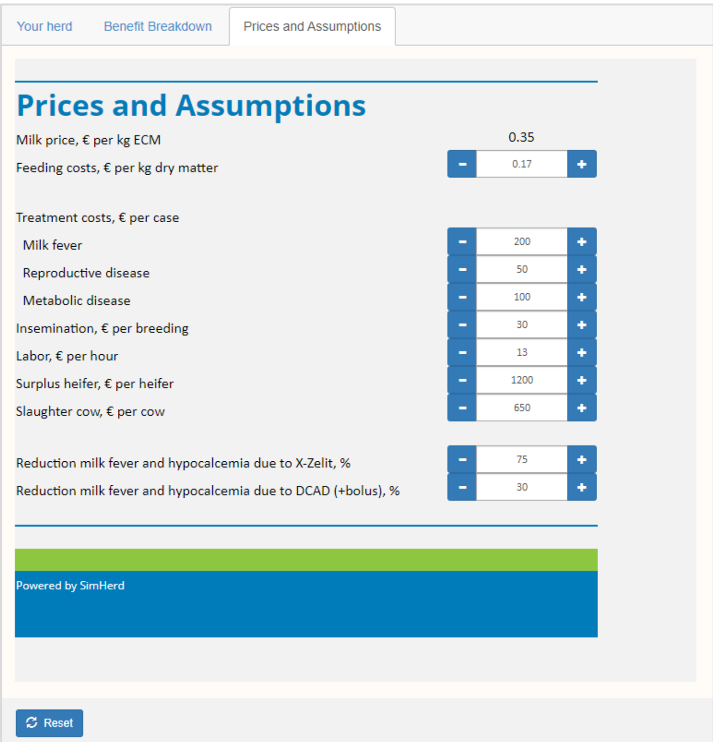

Figure 6: prices, costs and other assumptions

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Appendix: literature study on incidence and prevention

Level of hypocalcemia in dairy herds and efficiency of methods for prevention of hypocalcemia

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13/01/22

Subclinical hypocalcemia refers to cows that are clinically healthy, but with concentrations of Calcium (Ca) lower than measured in healthy cows. There is inconsistency in literature regarding the cut-off value of total Ca concentration in serum to define subclinical hypocalcemia. The most common cut-off value is a concentration of Ca in serum <2 mmol/L (Reinhardt et al. 2011). More recently, 2.15 mmol/L has been accepted as the cut-off value, as this threshold was determined using receiver operator characteristic analysis (e.g. Martinez *et al.* 2012; Kerwin *et al.*, 2019; Rodriguez *et al.*, 2017). Papers reporting levels of subclinical hypocalcemia are listed in table 1.

Table 1. Level of subclinical hypocalcemia reported for a range of countries.

Country	Threshold	Parity 1	Parity 2	Parity 3+	Sample time	Study size	Reference
USA	2.0 mmol/l	25 %	41 %	50 %	0 – 48 hr	480 herds 1462 cows	Reinhardt et al., 2011
Germany	2.0 mmol/l 2.1 mmol/l 2,2 mmol/l	6 % 14 % 36 %	29 % 45 % 63 %	60 % 66 % 80 %	0 - 48 hr	115 herds 1380 cows	Venjakob et al., 2017
Spain	2.15 mmol/L	14.3 %	85 %	85 %	24 - 48 hr	7 herds 664 cows	Rodriguez et al., 2017
Canada	2 mmol/l 2.15 mmol/l	2 % 21 %	32 % 62 %	80 % 90 %	<8 hr	7 herds 657 cows	Miltenburg, 2015
Denmark	2.15 mmol/l	26 %	52 %	59 %	0 – 72 hr	12 herds 83 cows	Skau, 2015
Denmark	2.0 mmol/l	0 %	35 %	52 %	0 – 24 hr	12 herds 275 cows	Pedersen and Christensen, 2016
France	2.0 mmol/L	16 %	57 %	57 %	12 – 24 hr	n.a. herds 106 cows	Gillet et al., 2016
Israel	1.9 mmol/L		4,9	40 %	8 – 20 hr	2 herds 633 cows	Gild et al, 2015
NZ - pasture	2.15			52 %		76 herds 1055 cows	Robert and McDougall, 2018

As observed in table 1, there are differences in the methods for detecting the level of subclinical hypocalcemia. Anyway, across countries and method there is a high stability in the reported frequencies. The proportion of cows with hypocalcemia is suggested to be 50 % across lactations.

Efficiency of anionic salt and X-Zelit for prevention of subclinical hypocalcemia

Despite the huge amount of literature references on subclinical hypocalcemia, the efficiency of the methods used for prevention are rarely described. Usually, the value of blood calcium is listed but that cannot be used for frequency studies on efficiency. Only literature where the frequency of hypocalcemia could be extracted is used in the following.

To estimate the efficiency of the DCAD, the most recent review of efficiency is the meta-analysis across 18 peer reviewed studies on the effect of anionic salt supplements in the dry period to prevent clinical hypocalcemia (Lean et al., 2019). The references used in this meta-analysis were all examined for information on frequency of hypocalcemia (table 2).

To estimate the efficiency of the X-Zelit (synthetic zeolite) all papers where this could be derived were used (Table 2).

The efficiency of the methods was calculated as (% cows above threshold in CONTROL GROUP minus % cows above threshold in EXPERIMENTAL GROUP) / % cows above threshold in CONTROL GROUP.

Table 2. Frequency of cows hypocalcemic in control or experiment group (DCAD or X-Zelit) and calculated efficiency.

Treatment	Control Group, SCH % of cows	Treatment Group SCH, % of cows	Efficiency, %	Threshold	Comment	Reference
X-Zelit	75	11	90	Ca < 2.0	Dose III+IV	Grabherr et al., 2009
X-Zelit	63	0	100	Ca < 2.0	Farm 1	Thilsing *et al.*, 2003
X-Zelit	100	0	100	Ca < 2.0	Farm 2	Thilsing *et al.*, 2003
X-Zelit	75	25	67	Ca < 2.0	Farm 3	Thilsing *et al.*, 2003
X-Zelit	55	21	62	Ca < 2.0	Farm 4	Thilsing *et al.*, 2003
X-Zelit	78	76	3	Ca < 2.0	Farm 5	Thilsing *et al.*, 2003
X-Zelit	78	15	81	Ca < 2.0	Farm 6	Thilsing *et al.*, 2003
X-Zelit	22,6	0	100	Ca < 2.0		Roche *et al.*, 2018
X-Zelit	60	5,2	91	Ca < 2.0		Pallesen *et al.*, 2008
X-Zelit	74	20	76	Ca < 2.15	Average day 0-3	Kerwin et al., 2019
AVERAGE X-ZELIT			**77**			
DCAD	58	40	29	Ca < 2.0		Leno *et al.*, 2017
DCAD	77	59	45			Rezak, 2014
DCAD	63	29	53	Ca < 1.0 mmol Ca+	DCAD -75 Control 189 Thresshold 1 mmol Ca+	Oetzel *et al.*, 1988
DCAD	98	90	8	Ca < 1.9	DCAD (-54-98 Control 202-461	Goff and Horst, 1997
DCAD	53	45	12	Ca < 2.0	DCAD -15 mEq/kg, Control 11 mEq/kg, average of first 2 days	Ramos-Nieves, 2009

DCAD	67	35	48	Ca < 2.0		Penner et al., 2008
DCAD	50	50	0	Ca < 2.0	138 vs 29 mEq/kg	Gulay et al., 2008
DCAD	50	19	62	Ca < 2.0		
AVERAGE DCAD			**32**			

The average efficiency across study is 77% for X-Zelit and 32% for the DCAD supplementation in close-up group. These values are used as default settings.

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