REDNEX

Challenges to modelling intermediary nitrogen metabolism

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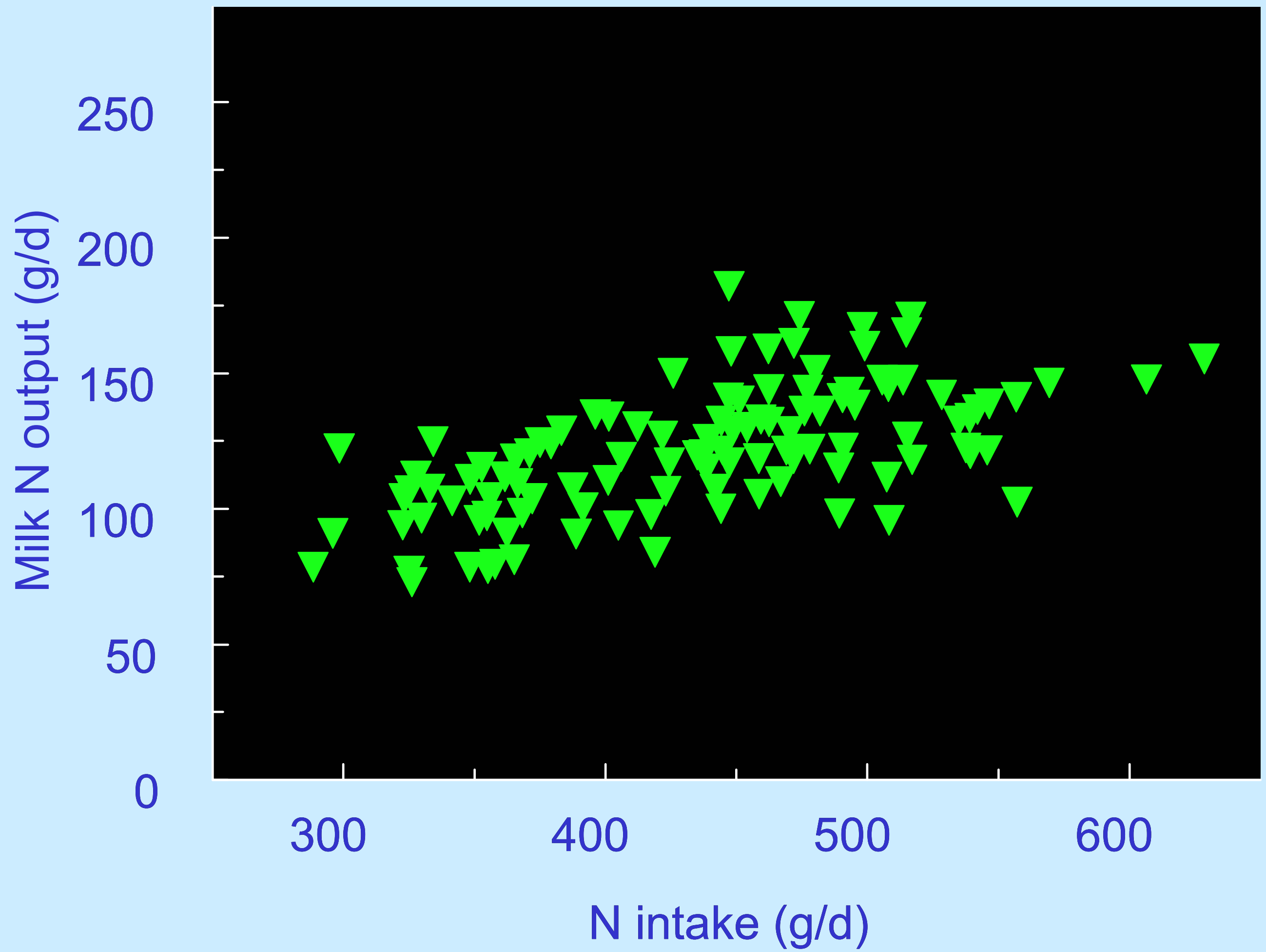
Overview

1. N metabolism in the dairy cow
2. Kinetic and process-based simulation modelling
3. Review: kinetic models
4. Review: simulation models
5. Future challenges

Variation in milk N efficiency

- Low conversion of dietary N into milk N (0.15 – 0.40)



Kebreab et al. (2002)

Variation in milk N efficiency

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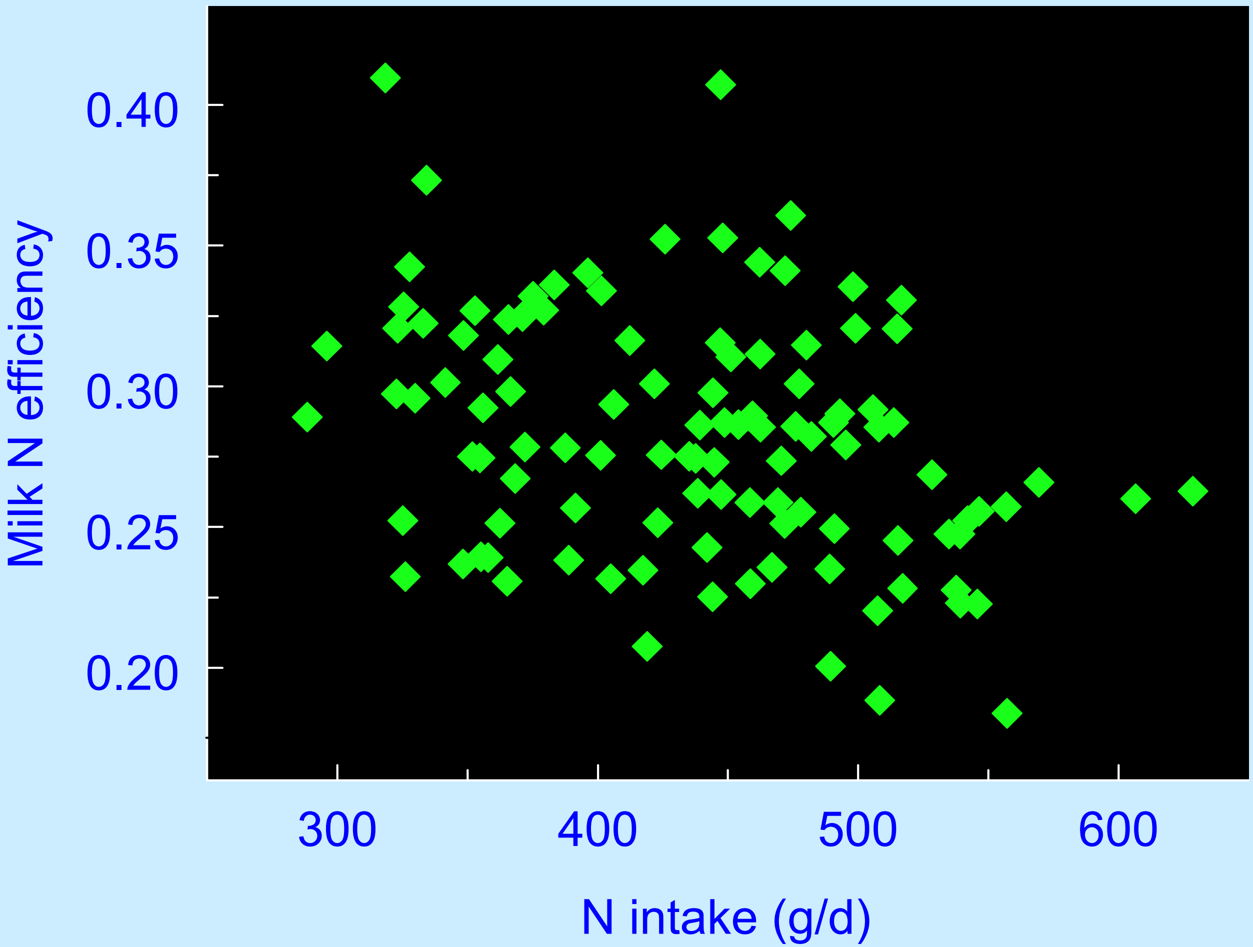


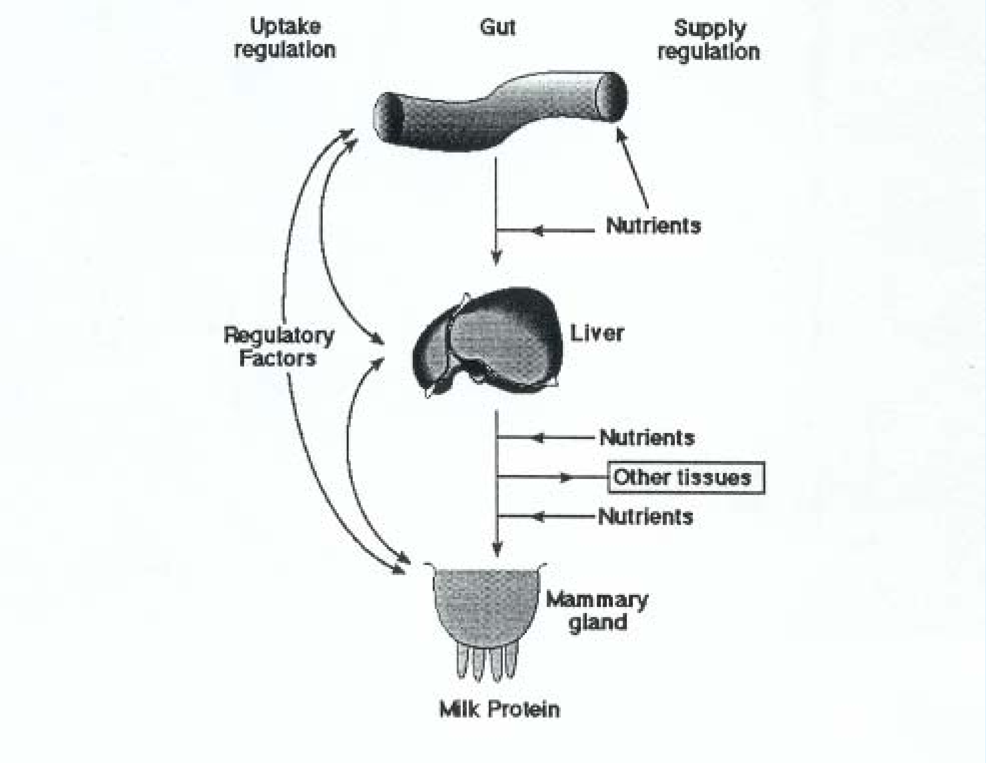
Kebreab et al. (2002)

Variation in intermediary N metabolism

- 0.05 to 0.80 of all AA removed by gut
  - No or low losses of His
  - Medium losses of Leu, Thr
  - High losses of non-essential AA
- 0.15 to 0.70 of all AA removed by liver
  - No or low losses of branched-chain AA and Lys
  - Substantial losses of His, Met, Phe, Thr
- 0 to 0.60 of all AA removed by mammary gland
  - No or low losses of His, Met, Phe, Trp
  - Substantial losses of branched-chain AA and Lys
  - Apparent synthesis of non-essential AA

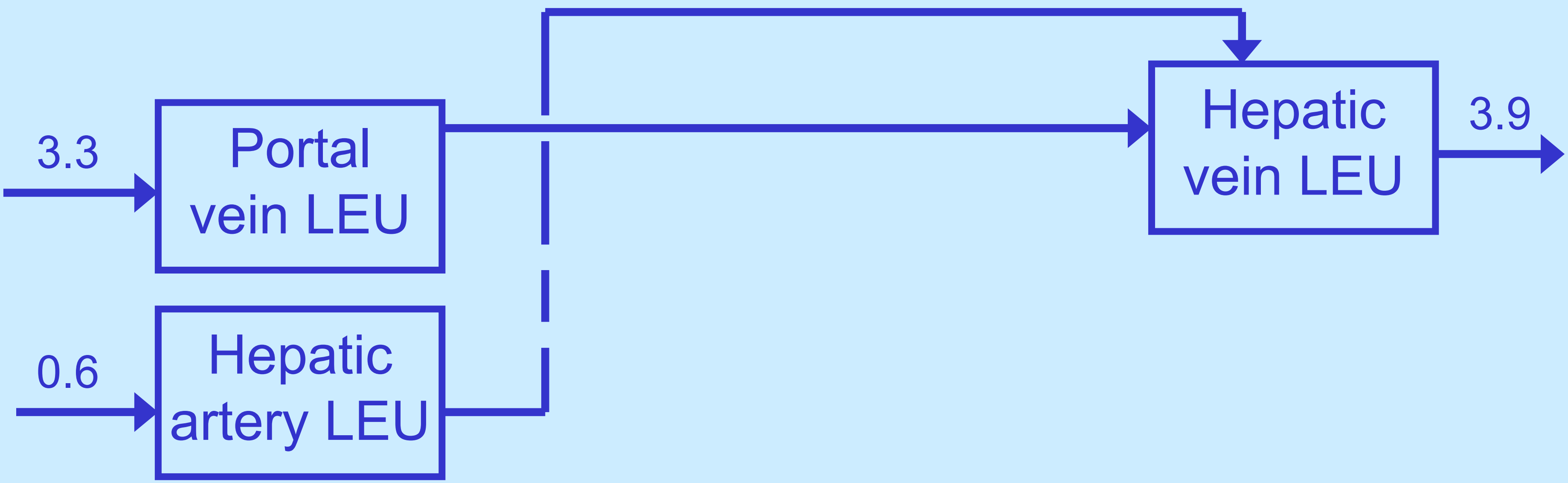
Lapierre et al. (2005)

Organs of intermediary N metabolism



Flows more detailed using isotopic data than with net fluxes

mmol/h; France et al. (1999)



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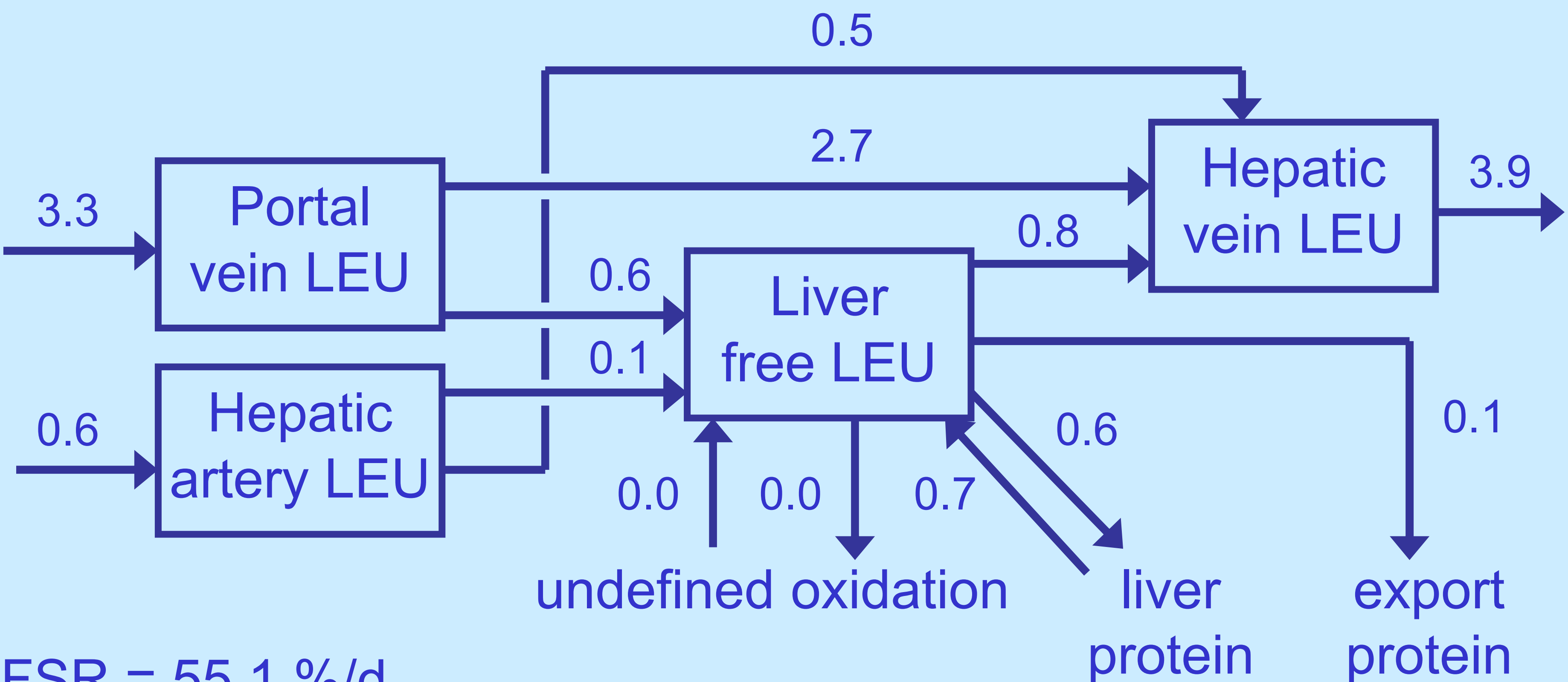
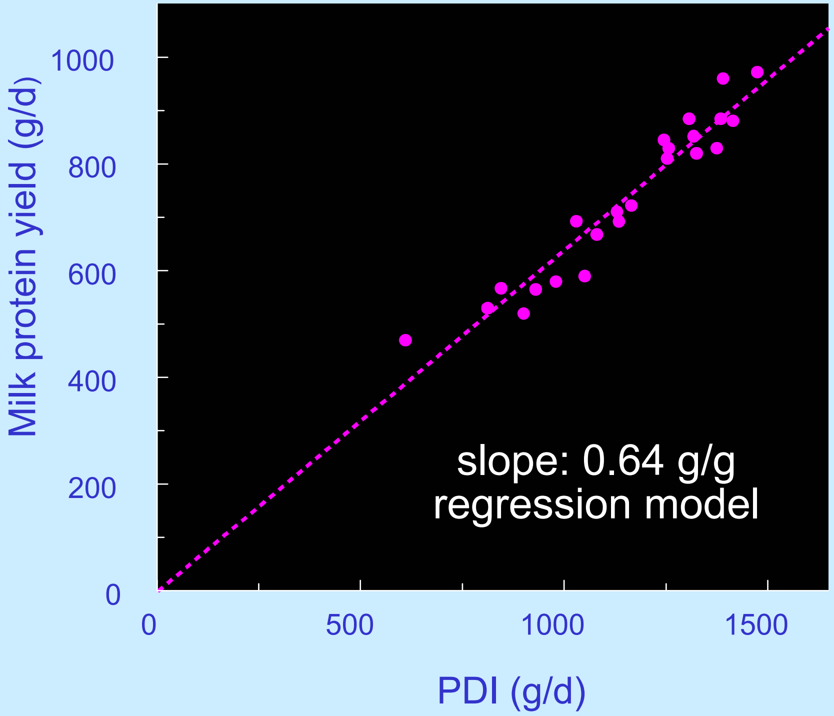
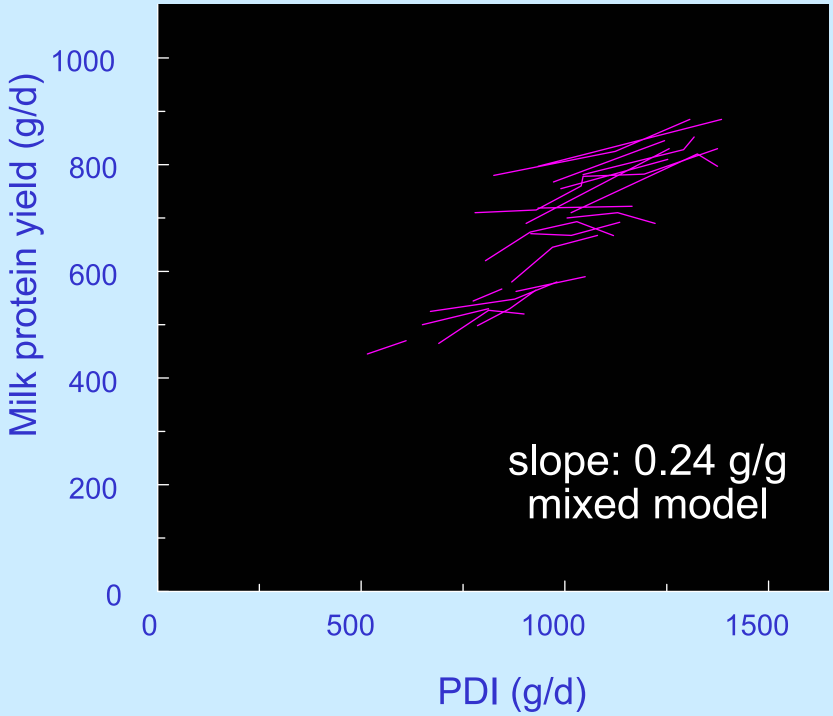


FSR = 55.1 %/d

Limitations of protein evaluation systems





Cant (2005)

Limitations of protein evaluation systems

- Current protein evaluation systems are requirements based
- Various key transfer routes are represented using fixed values
  - 150 g microbial protein/kg fermentable organic matter
  - efficiency of metabolisable protein into milk protein 0.64-0.68
- Empirical basis hampers inclusion of new findings
- Response prediction systems require mechanistic basis
  - Representation of principal AA in at least gut wall, liver and mammary gland required in future systems

Rate:state formalism

$dQ_1/dt = f_1(\mathbf{Q}; \mathbf{P})$

$dQ_2/dt = f_2(\mathbf{Q}; \mathbf{P})$

•   •

•   •

$dQ_n/dt = f_n(\mathbf{Q}; \mathbf{P})$

Newton's 2nd law of motion

1st law of thermodynamics

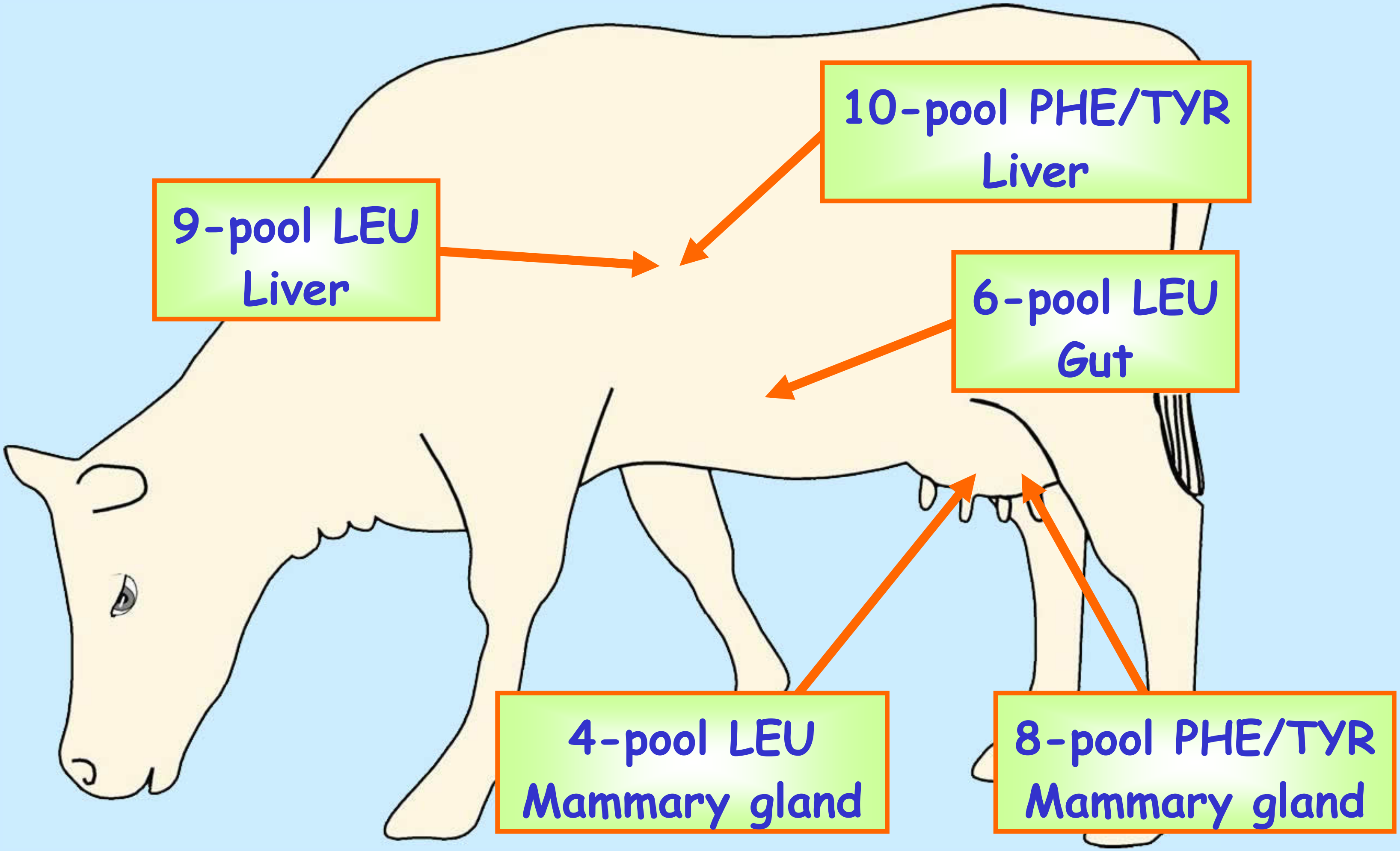
Law of mass conservation

- Solution
  - Type I: In steady state, obtain solutions by setting differentials to zero and manipulating to give algebraic expression for each process
  - Type II: In non-steady state, solve rate:state equations analytically (simple cases)
  - Type III: In non-steady state, solve rate:state equations numerically (complex cases)

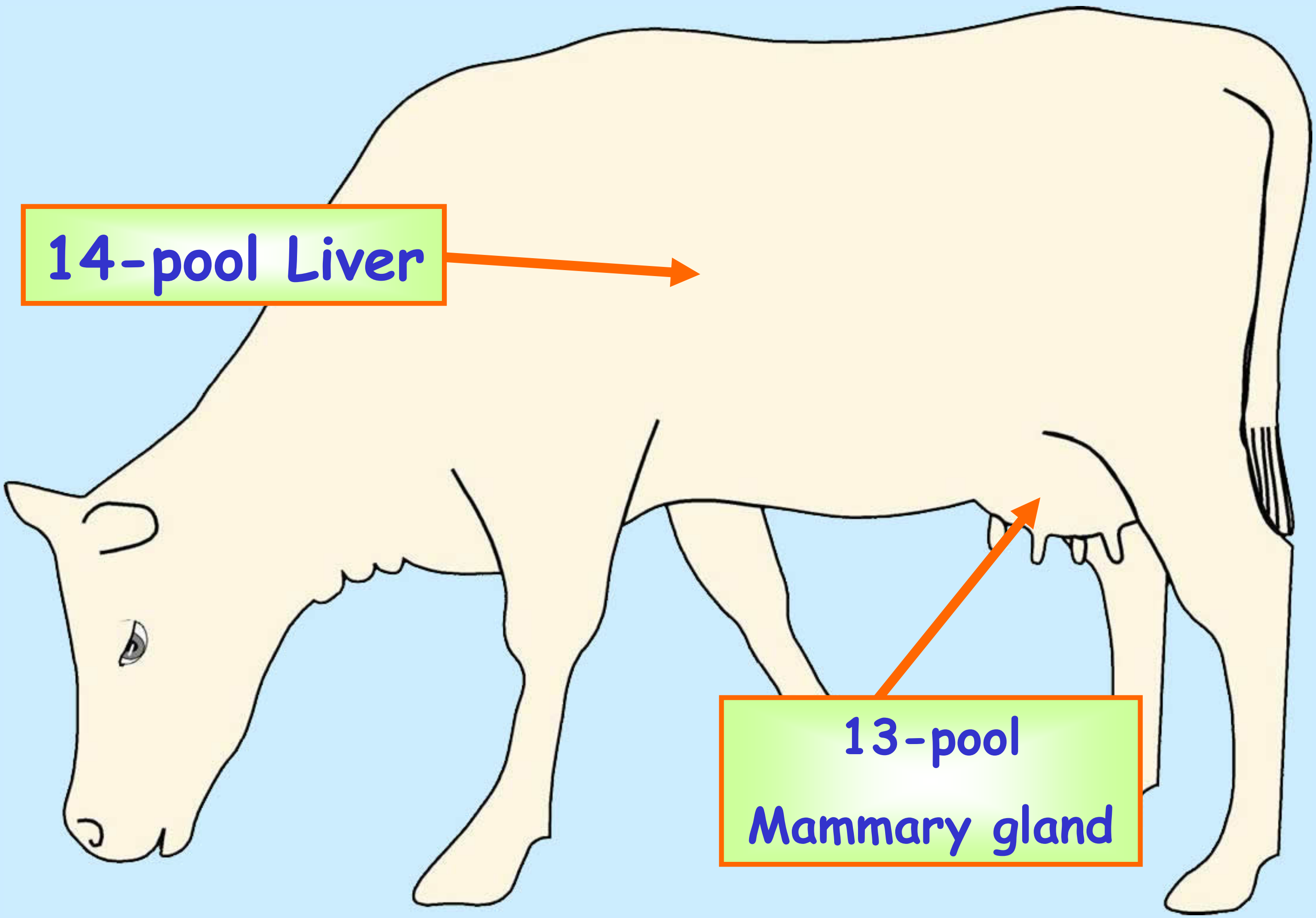
Interplay between kinetic and simulation modelling

- Kinetic models allow quantitative interpretation of data required to develop and test process-based simulation models (parameter estimation, model evaluation)
- Kinetic models can help elucidate mechanisms in response to variation in nutrient supply
- Unlike process-based models, kinetic models cannot predict responses to change in nutrient supply
- Thus kinetic models provide 'pieces of the jigsaw': information required to develop and test process-based simulation models

Kinetic models

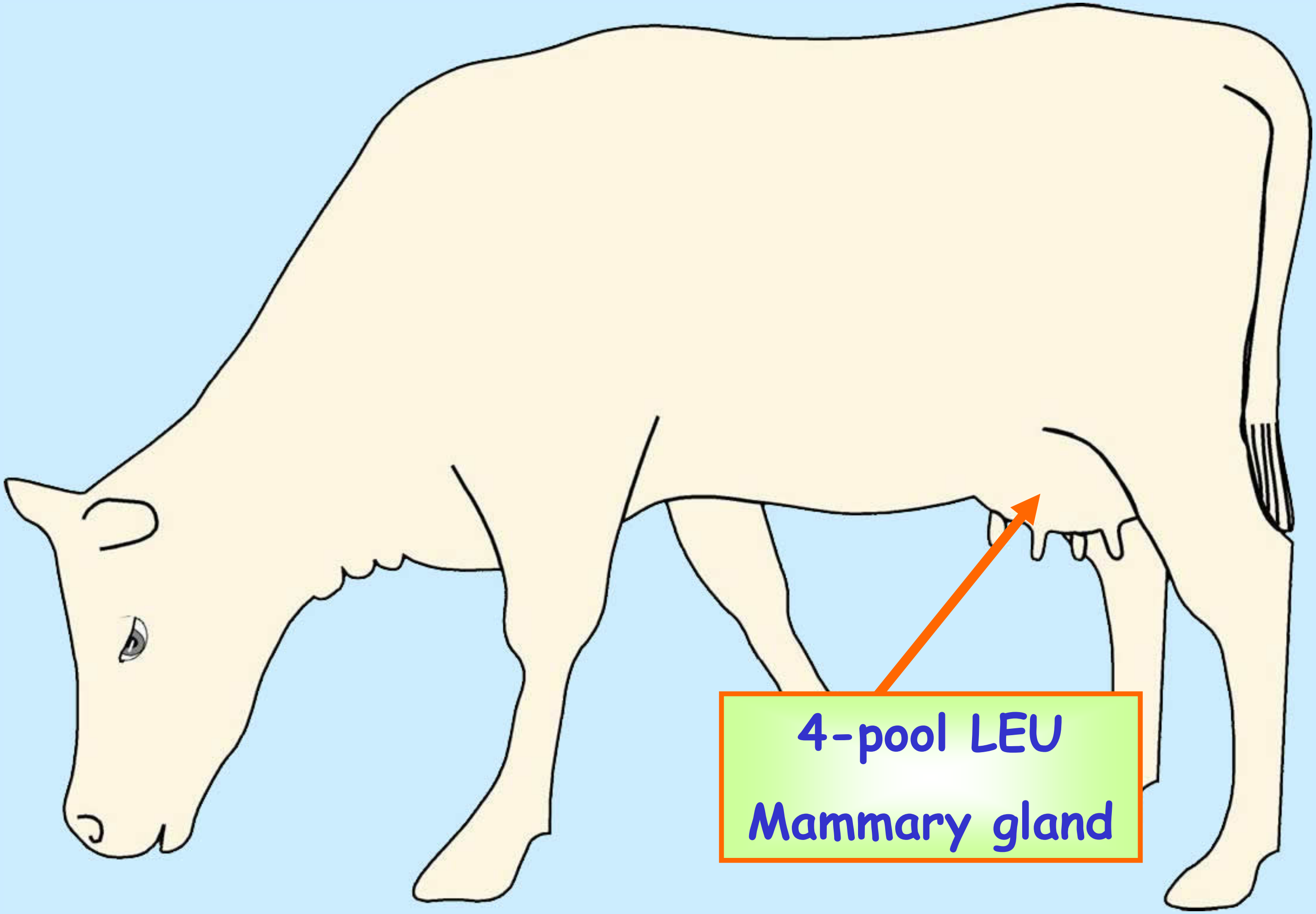


Simulation models

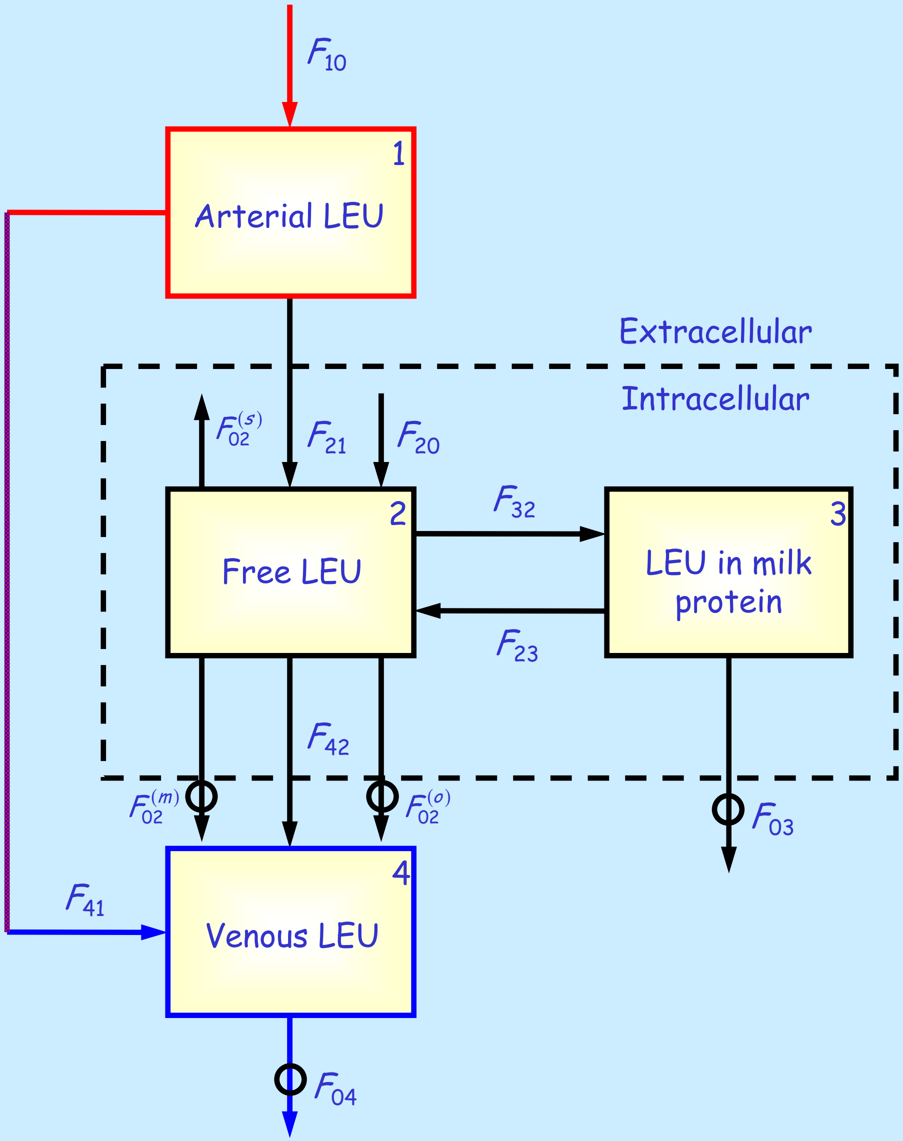


Kinetic models

France et al. (1995)



Flow diagram



Differential equations

For total leucine:

$$\frac{dQ_1}{dt} = F_{10} - F_{21} - F_{41} \tag{4.1}$$

$$\frac{dQ_2}{dt} = F_{20} + F_{21} + F_{23} - F_{02}^{(m)} - F_{02}^{(o)} - F_{02}^{(s)} - F_{32} - F_{42} \tag{4.2}$$

$$\frac{dQ_3}{dt} = F_{32} - F_{03} - F_{23} \tag{4.3}$$

$$\frac{dQ_4}{dt} = F_{41} + F_{42} - F_{04} \tag{4.4}$$

and for labelled leucine:

$$\frac{dq_1}{dt} = I - e_1\left(F_{21} + F_{41}\right) \tag{4.5}$$

$$\frac{dq_2}{dt} = e_1F_{21} + e_3F_{23} - e_2\left(F_{02}^{(m)} + F_{02}^{(o)} + F_{02}^{(s)} + F_{32} + F_{42}\right) \tag{4.6}$$

$$\frac{dq_3}{dt} = e_2F_{32} - e_3\left(F_{03} + F_{23}\right) \tag{4.7}$$

$$\frac{dq_4}{dt} = e_1F_{41} + e_2F_{42} - e_4F_{04} \tag{4.8}$$

Algebraic solution

When the system is in steady state with respect to both total and labelled leucine, the derivative terms in the differential equations are zero. Algebraic manipulation gives:

$$F_{02}^{(s)} = I / e_3 - \tilde{F}_{02}^{(m)} - F_{02}^{(o)} - \tilde{F}_{03} - e_4 \tilde{F}_{04} / e_3 \quad (4.16)$$

$$F_{10} = I / e_1 \quad (4.17)$$

$$F_{20} = (1/e_3 - 1/e_1) I + (e_3 - e_4) \tilde{F}_{04} / e_3 \quad (4.18)$$

$$F_{21} = I / e_1 - (e_3 - e_4) \tilde{F}_{04} / (e_3 - e_1) \quad (4.19)$$

$$F_{32} - F_{23} = \tilde{F}_{03} \quad (4.20)$$

$$F_{41} = (e_3 - e_4) \tilde{F}_{04} / (e_3 - e_1) \quad (4.21)$$

$$F_{42} = (e_1 - e_4) \tilde{F}_{04} / (e_1 - e_3) \quad (4.22)$$

where the italics denotes steady state values of flows and enrichments and the tilde indicates an experimentally measured flow.

Application

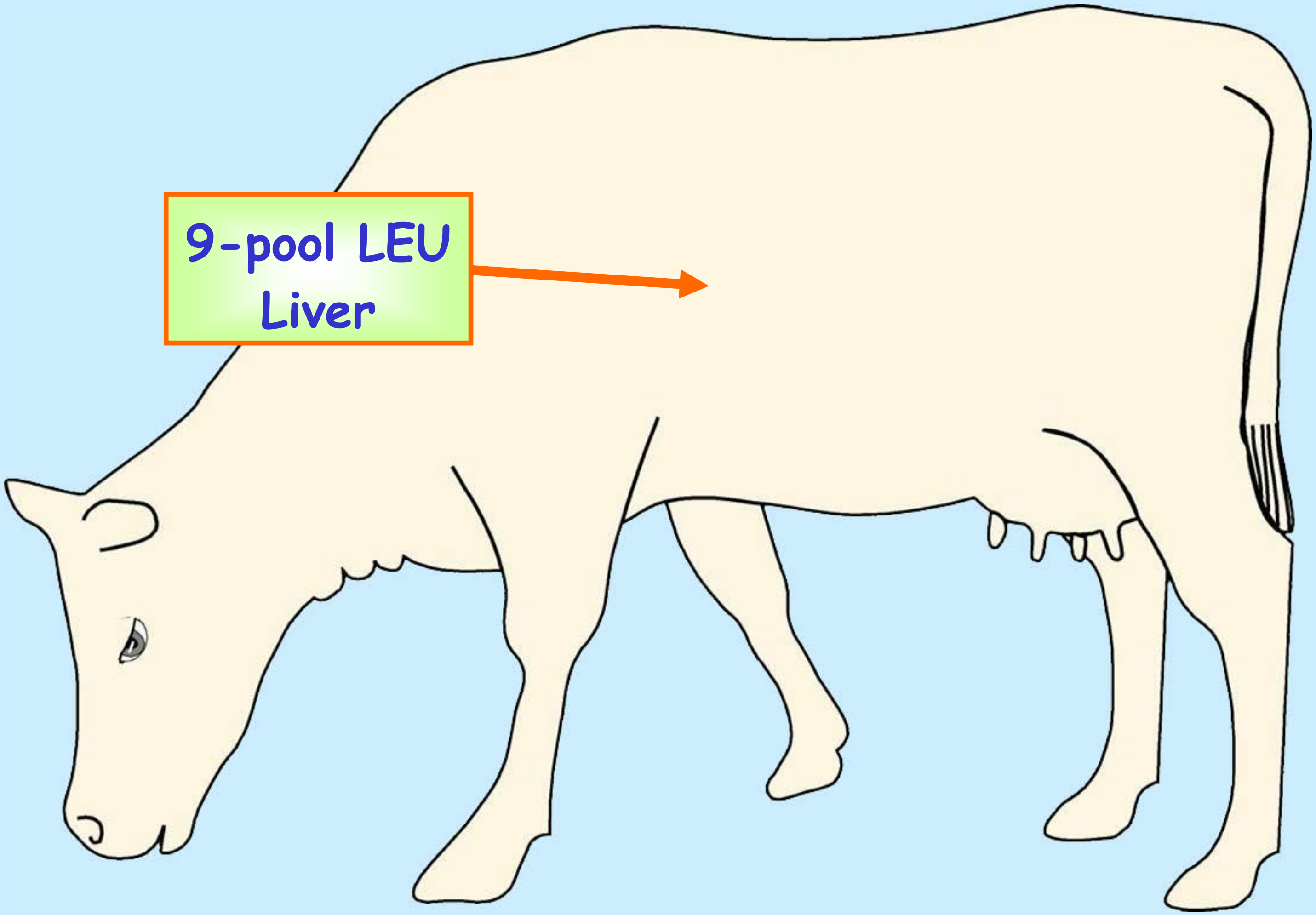
Leucine uptake and partition by the mammary gland

		Cow number		
		1	2	3
Dietary CP (g/kg)		130	130	155
Flow (μmol/min)	$F_{02}^{(o)}$	0	0	73
	$F_{02}^{(s)}$	**91**	**62**	**256**
	F_{10}	785	874	1156
	F_{20}	**146**	**67**	**256**
	F_{21}	524	607	755
	F_{23}	42	48	42
	F_{32}	421	478	421
	F_{41}	260	267	401
	F_{42}	200	182	303

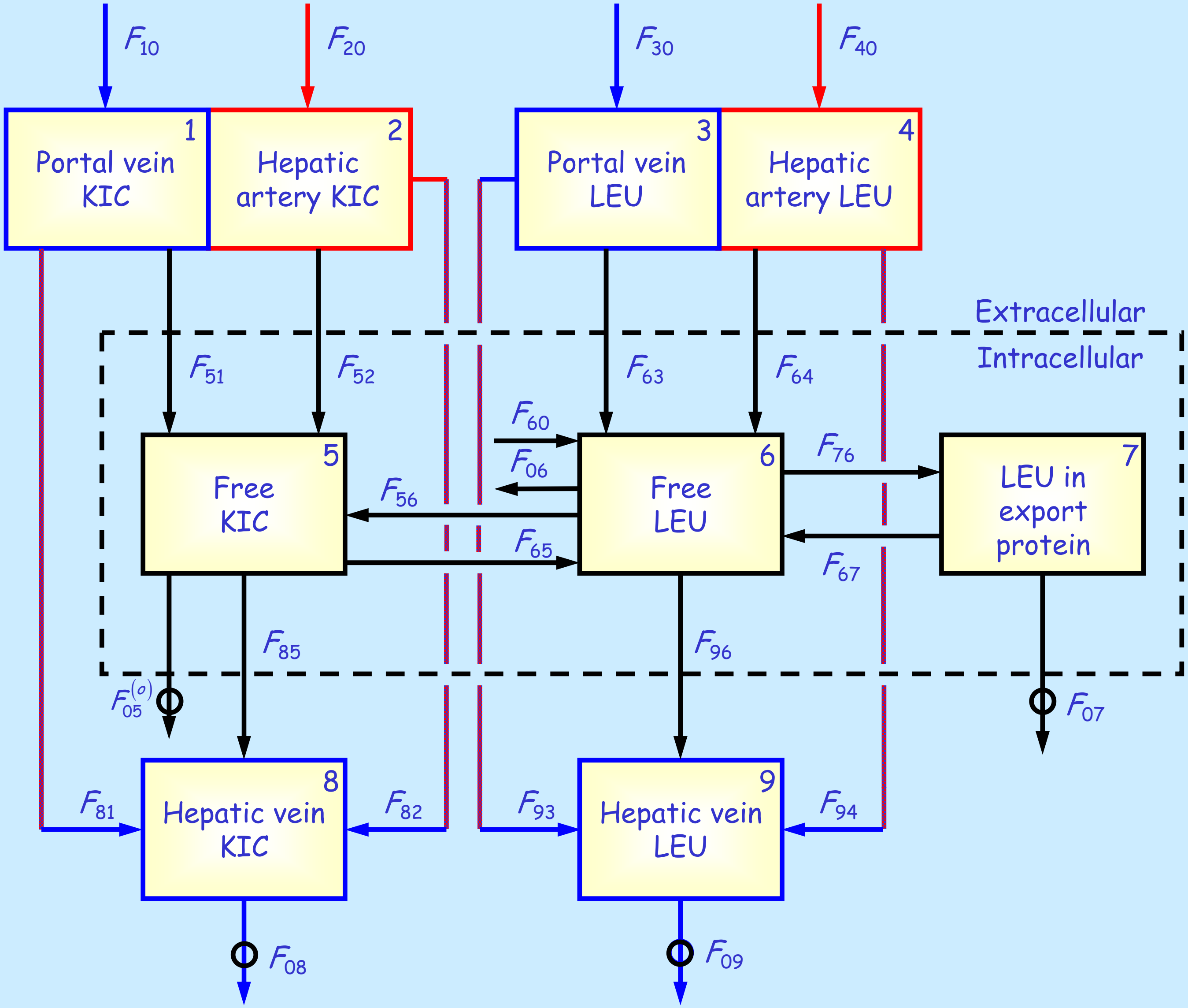
$F_{02}^{(s)}$, Constitutive protein synthesis; F_{20}, Constitutive protein degradation.

Kinetic models

France et al. (1999)



Flow diagram



Application

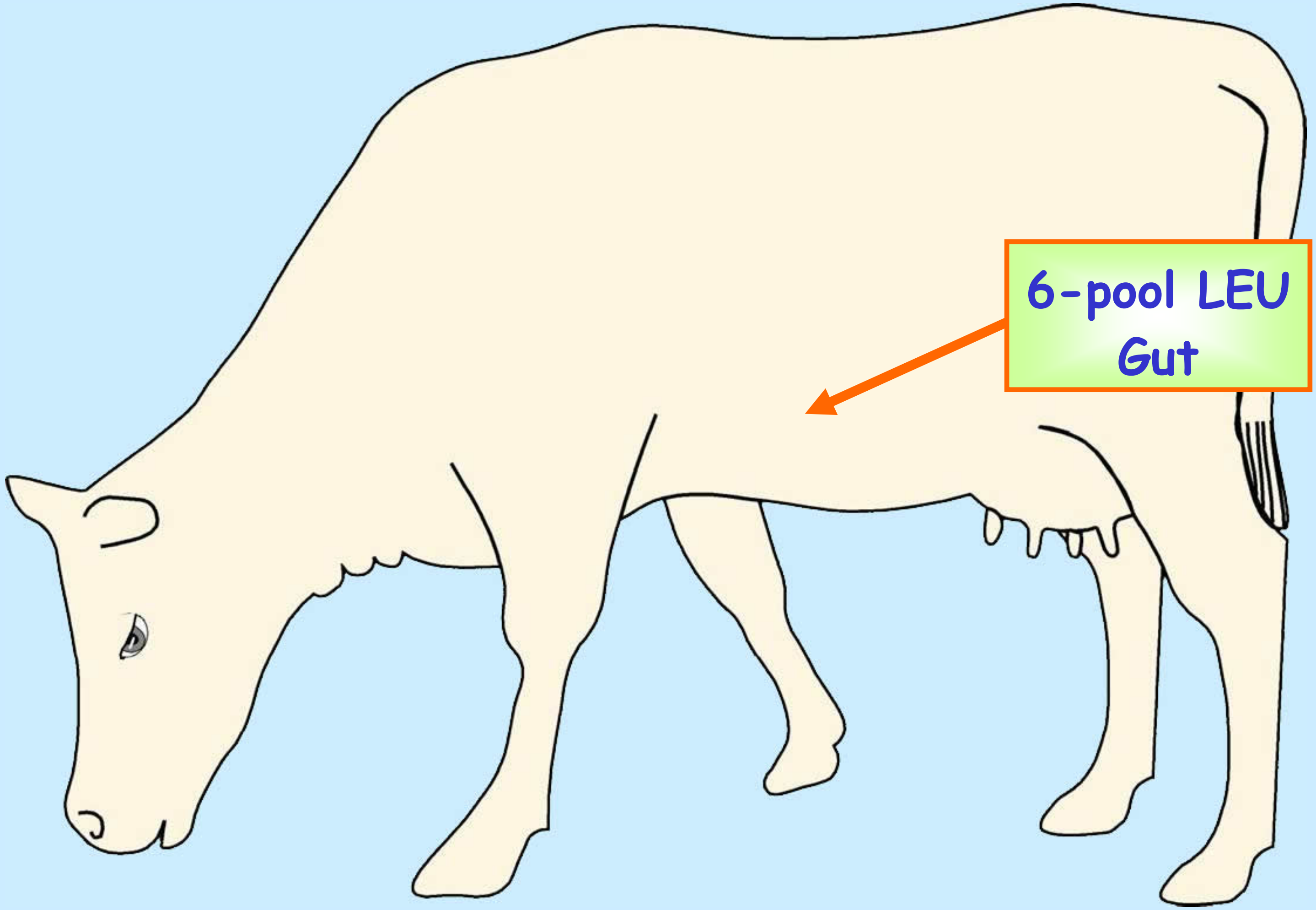
Leucine uptake and partition by the liver

		Cow number			
		6044/3	6188/4	6093/6	6062/8
Flow (μmol/min)	F_{10}	141	135	134	86
	F_{20}	25	31	13	26
	F_{30}	3285	2520	2474	2368
	F_{40}	559	547	229	686
	F_{51}	141	135	134	86
	F_{85}	137	155	126	99
	F_{56}	5	3	3	4
	F_{65}	33	14	12	1
	F_{63}	**597**	**541**	**438**	**381**
	F_{64}	102	117	41	111
	F_{93}	2688	1979	2037	1987
	F_{94}	457	430	189	576
	F_{96}	750	806	528	764
	F_{06}	**593**	**541**	**430**	**217**
	F_{60}	675	736	529	551

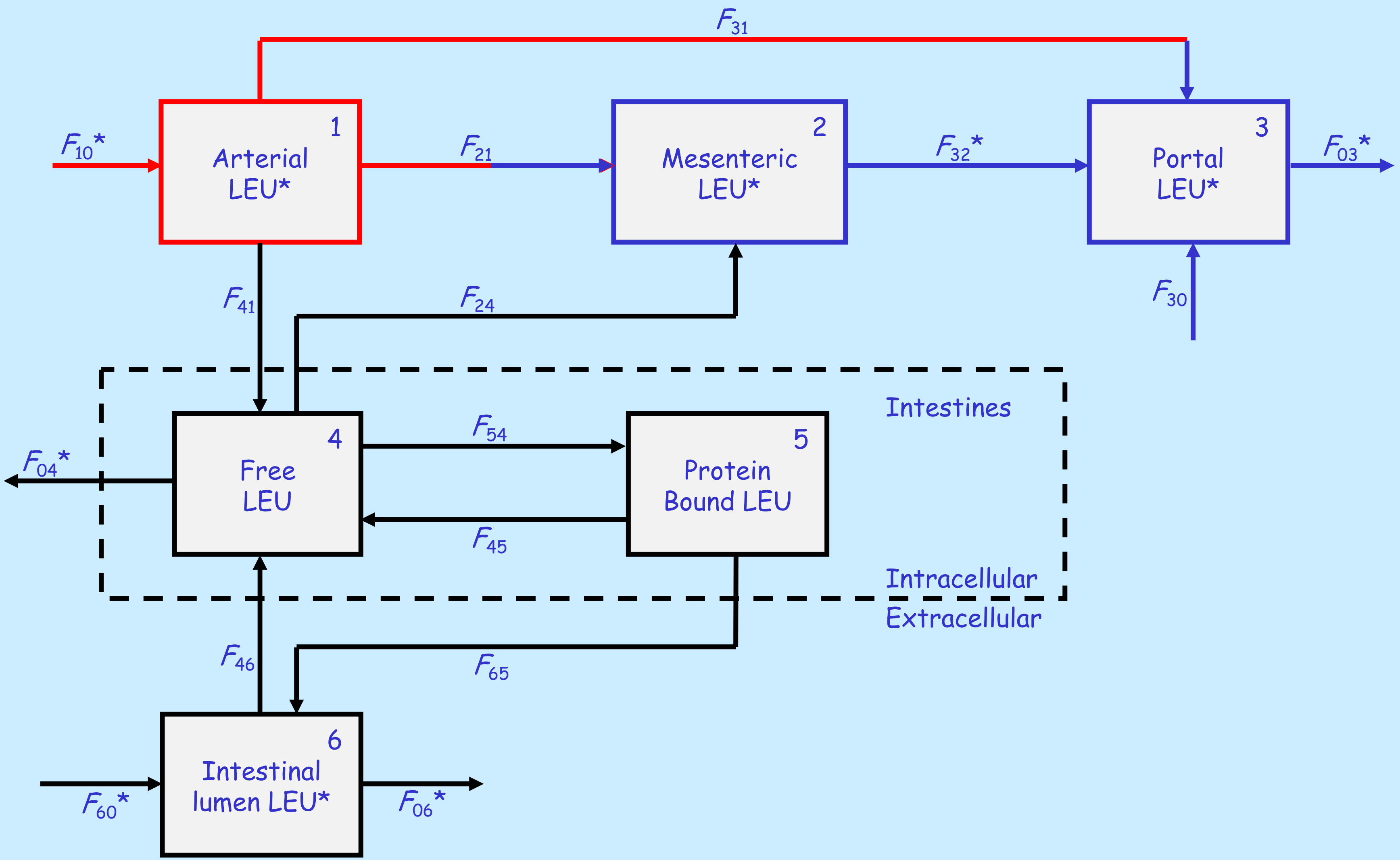
F_{63}, LEU uptake from portal vein; F_{06}, Constitutive protein synthesis.

Kinetic models

France et al. , in prep

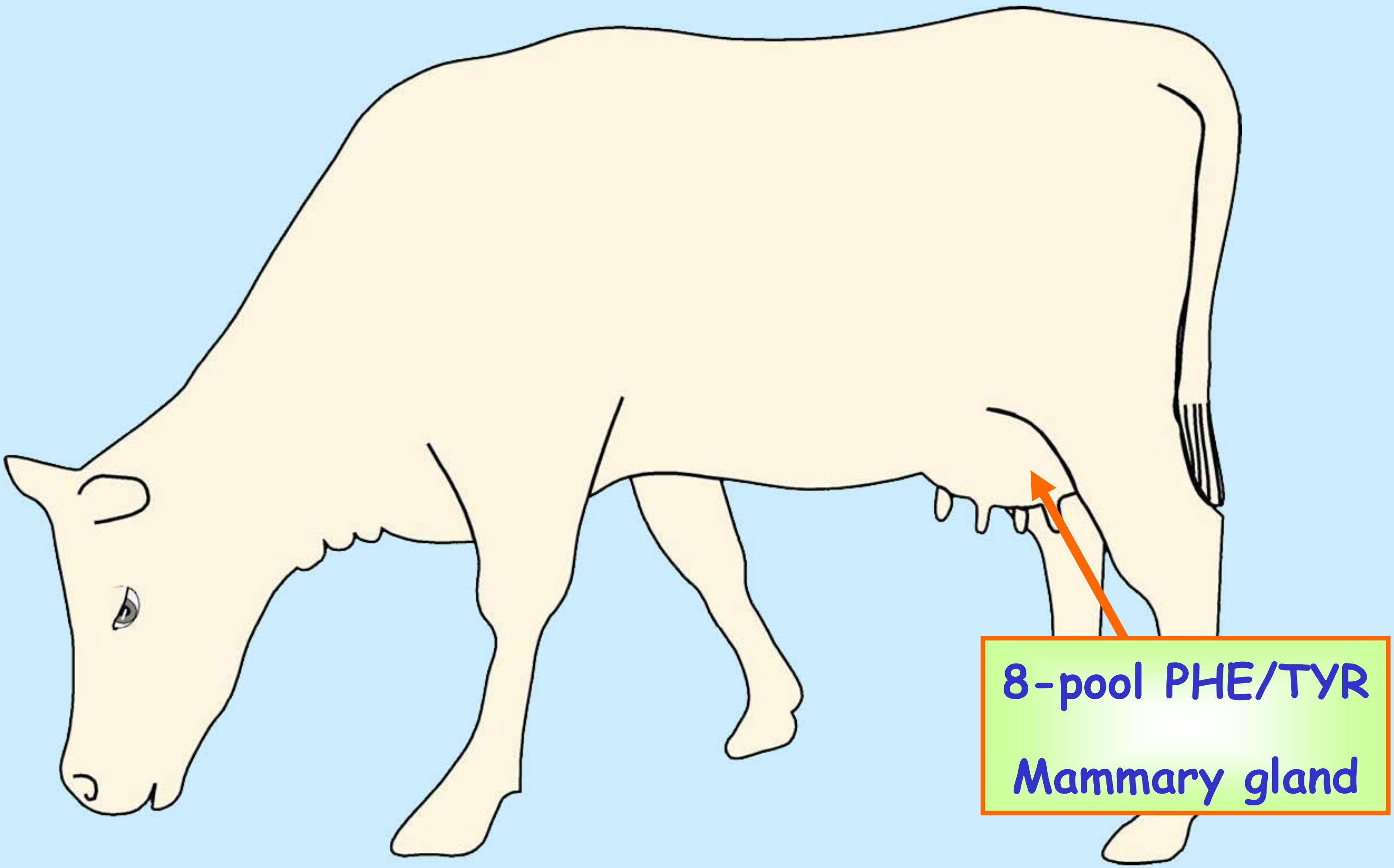


Flow diagram

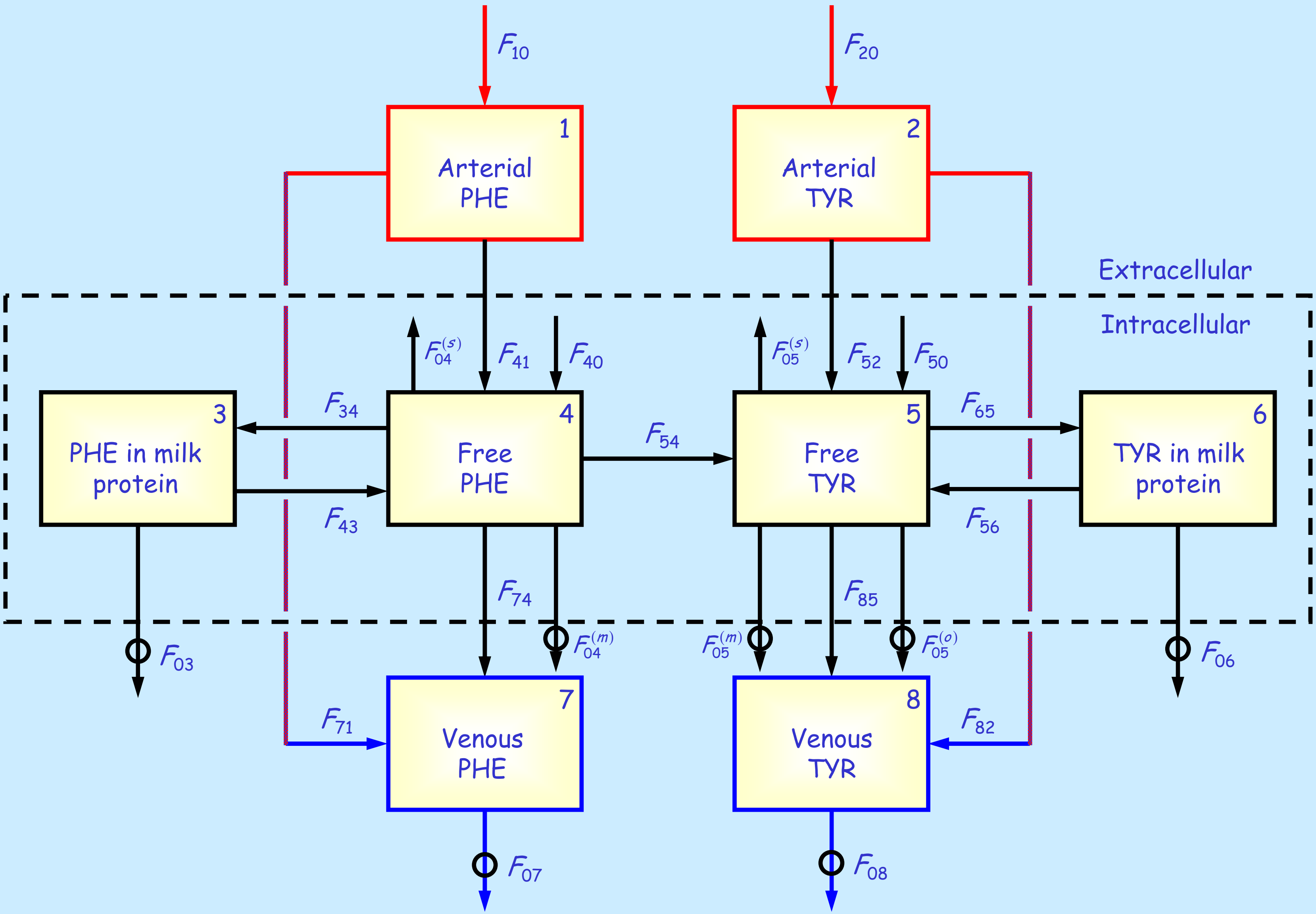


Kinetic models

Crompton et al., in prep



Flow diagram



Application

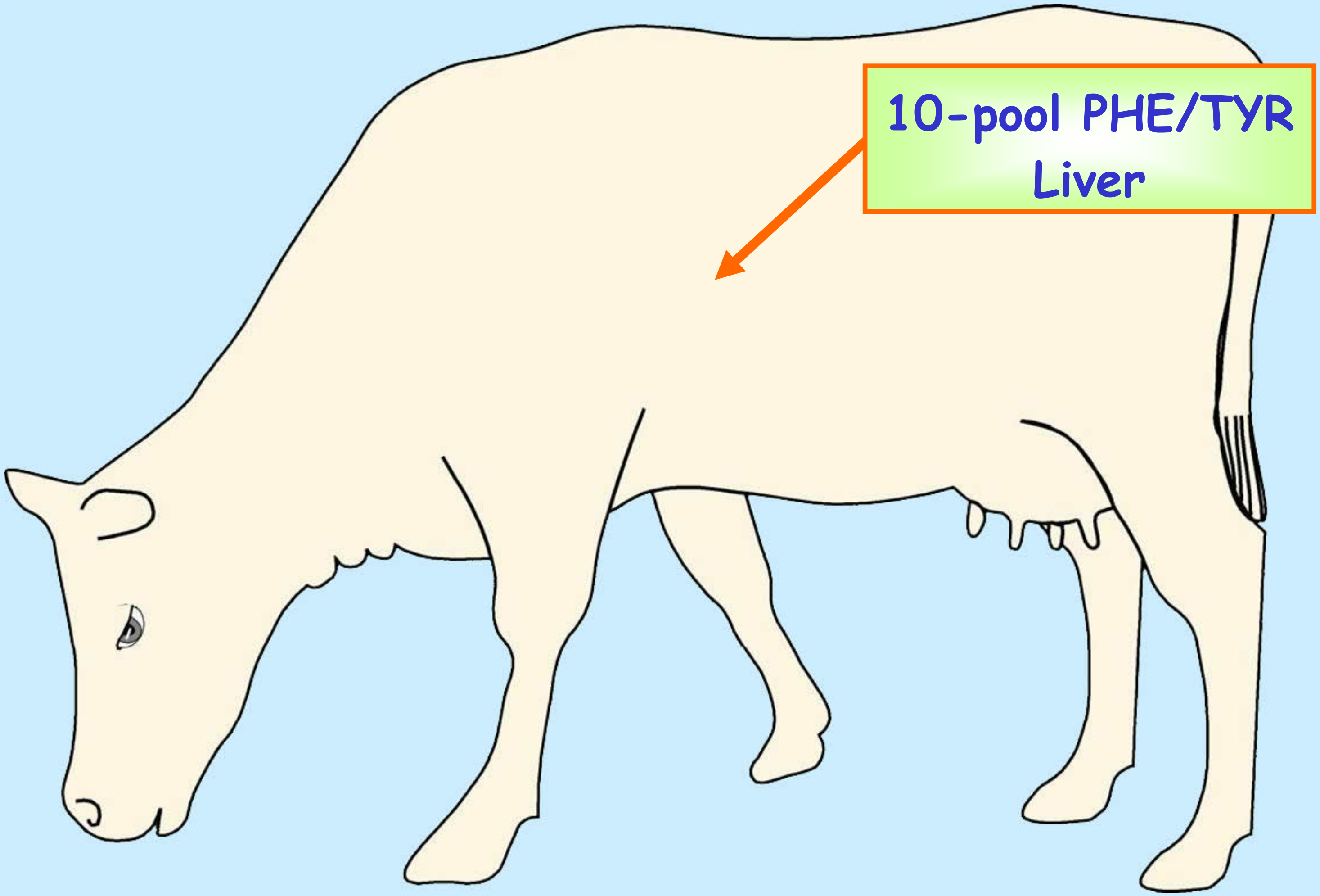
Phenylalanine and tyrosine uptake and partition by the mammary gland

		Cow number			
		A	B	C	D
Flow (μmol/min)	F_{10}	202	222	250	273
	F_{20}	184	205	269	251
	F_{34}-F_{43}	69	65	99	100
	F_{65}-F_{56}	71	67	101	103
	F_{71}	127	97	142	159
	F_{41}	**75**	**124**	**108**	**114**
	F_{74}	9	37	5	18
	F_{82}	101	87	142	136
	F_{52}	83	119	126	115
	F_{85}	21	29	17	24
	$F_{05}^{(s)}$	51	105	116	69
	F_{54}	**6**	**0**	**10**	**1**
	$F_{04}^{(s)}$	25	81	61	49
	F_{40}	34	52	67	53
	F_{50}	55	89	97	83

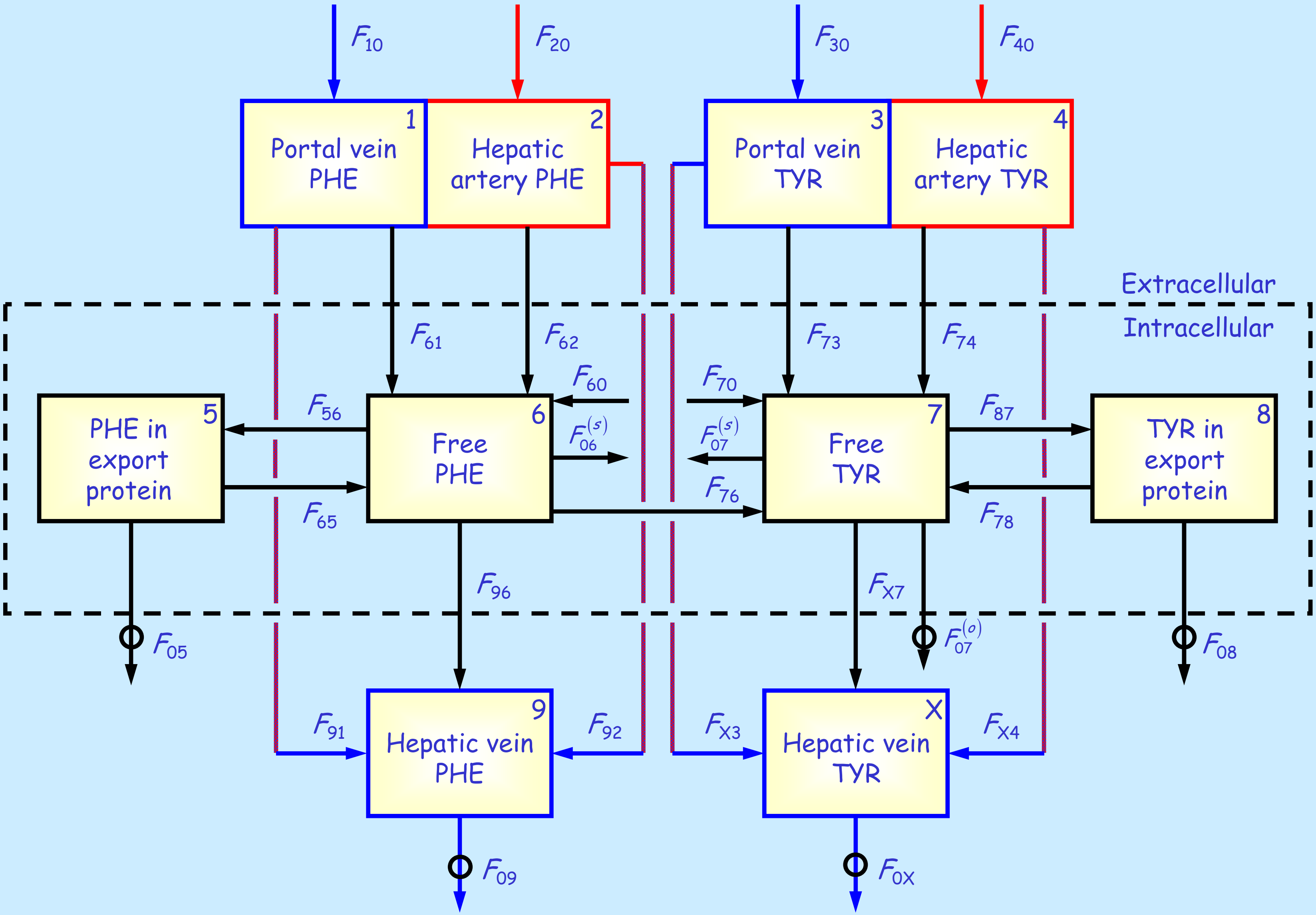
F_{41}, PHE uptake; F_{54}, Conversion of PHE to TYR.

Kinetic models

Crompton et al., in prep



Flow diagram



Application

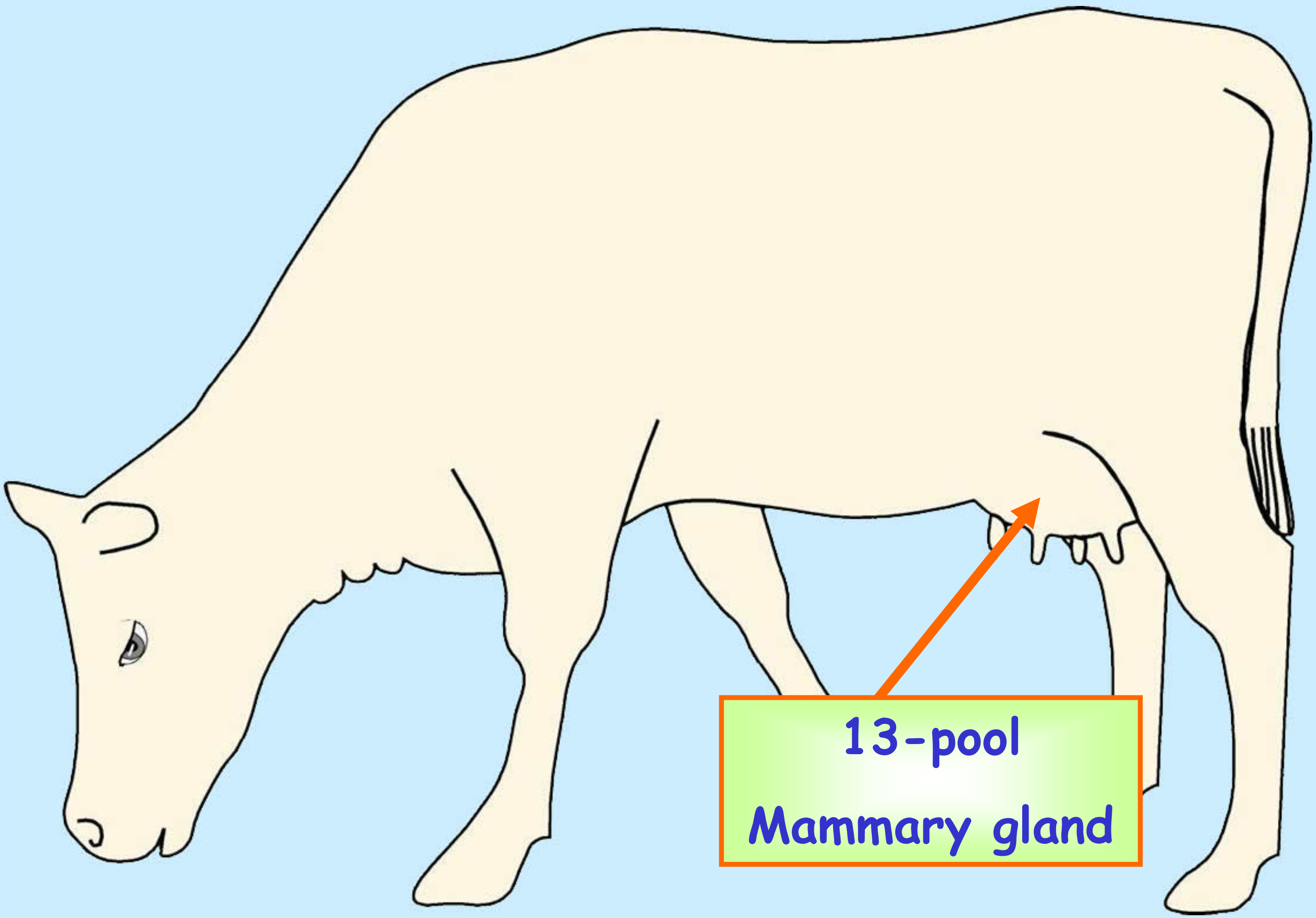
Phenylalanine and tyrosine uptake and partition by the liver

		Cow number			
		323/14	341/31	6132/41	
Flow (μmol/min)	F_{10}	2403	1768	1806	
	F_{20}	676	804	205	
	F_{30}	2486	1513	1763	
	F_{40}	756	701	215	
	$F_{56} - F_{65}$	34	34	34	
	F_{73}	771	386	552	
	F_{61}	**874**	**373**	**615**	
	F_{62}	**246**	**169**	**70**	
	F_{91}	1529	1457	1119	
	F_{92}	430	662	127	
	F_{96}	636	154	454	
	F_{76}	**80**	**39**	**49**	
	F_{X3}	1715	1177	1155	
	F_{X4}	522	545	141	
	F_{X7}	622	319	427	

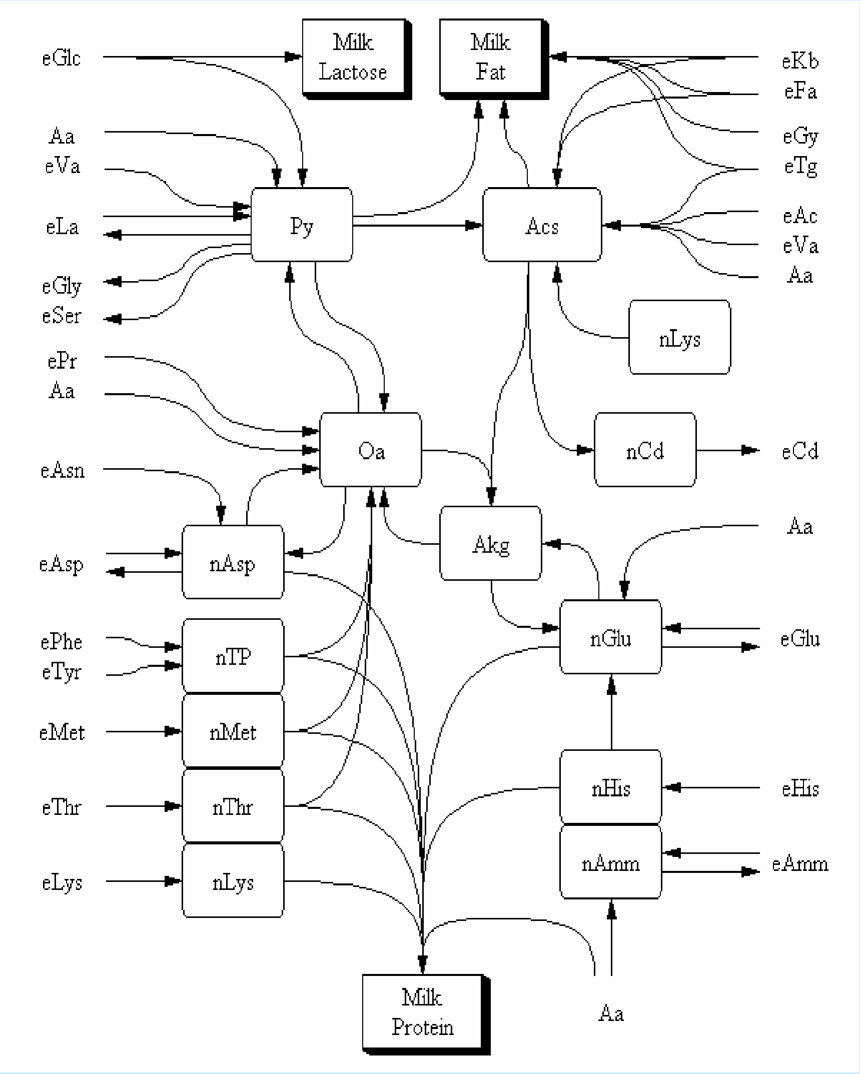
F_{61} and F_{62}, PHE uptake from portal vein and hepatic artery; F_{76}, Conversion of PHE to TYR.

Simulation models

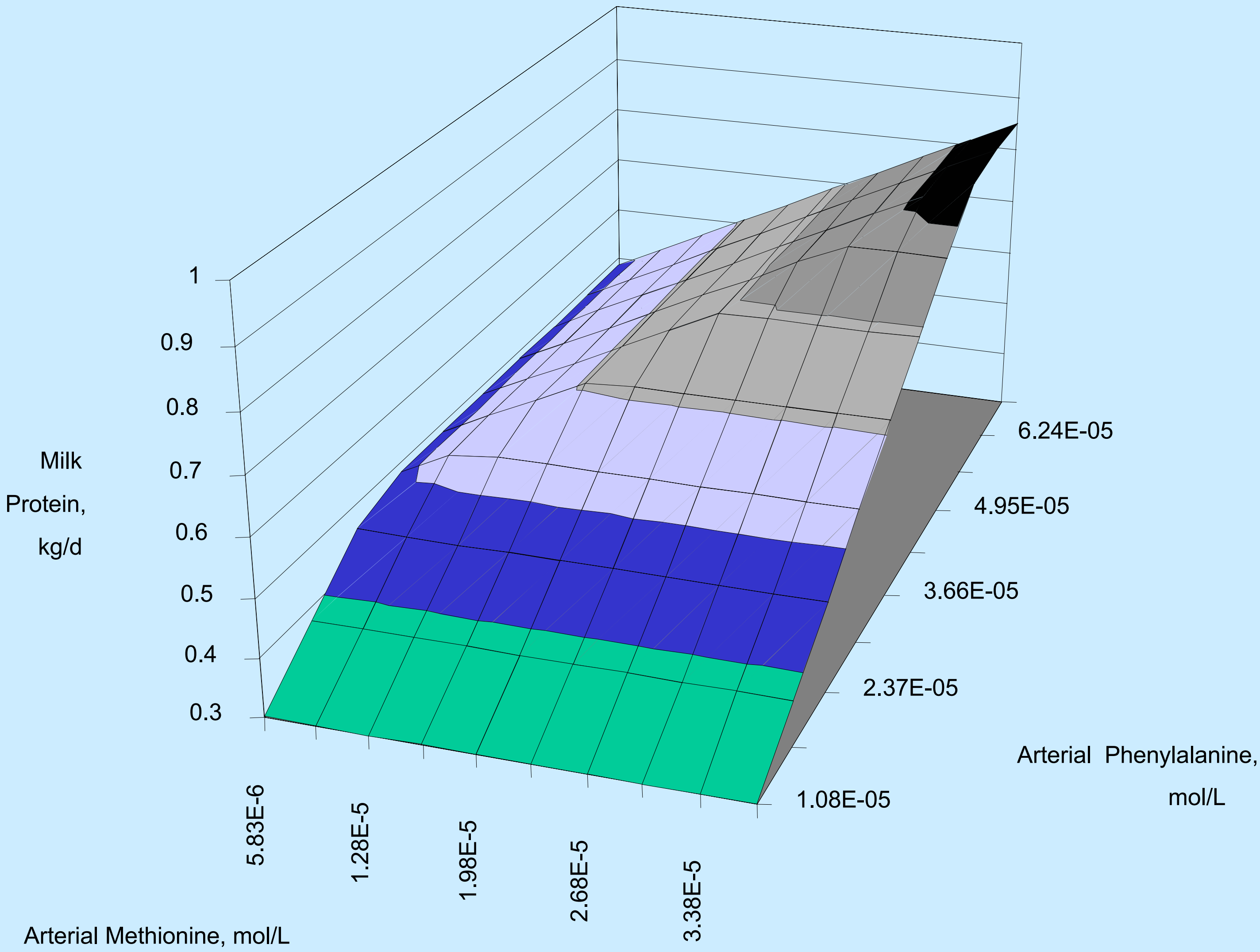
Hanigan et al. (2001)



Flow diagram

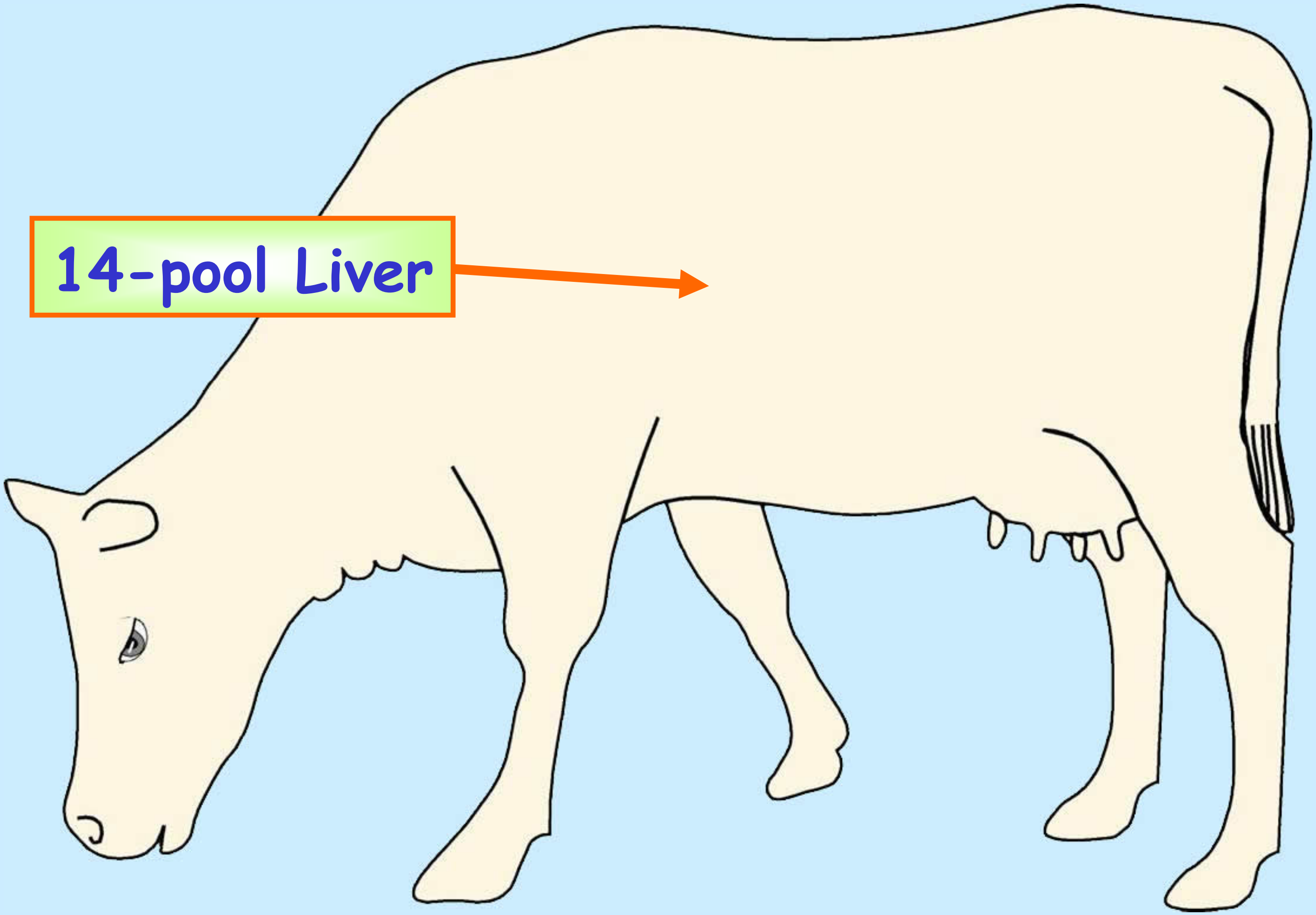


Application

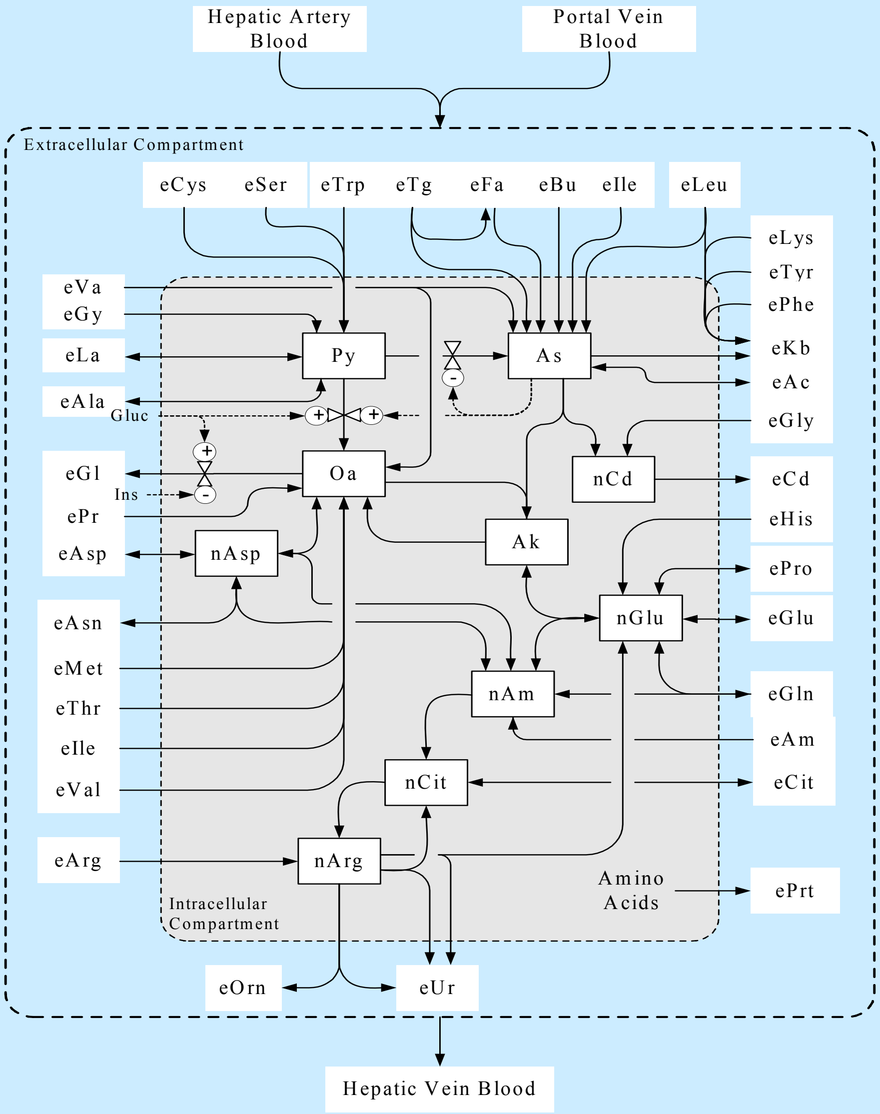


Simulation models

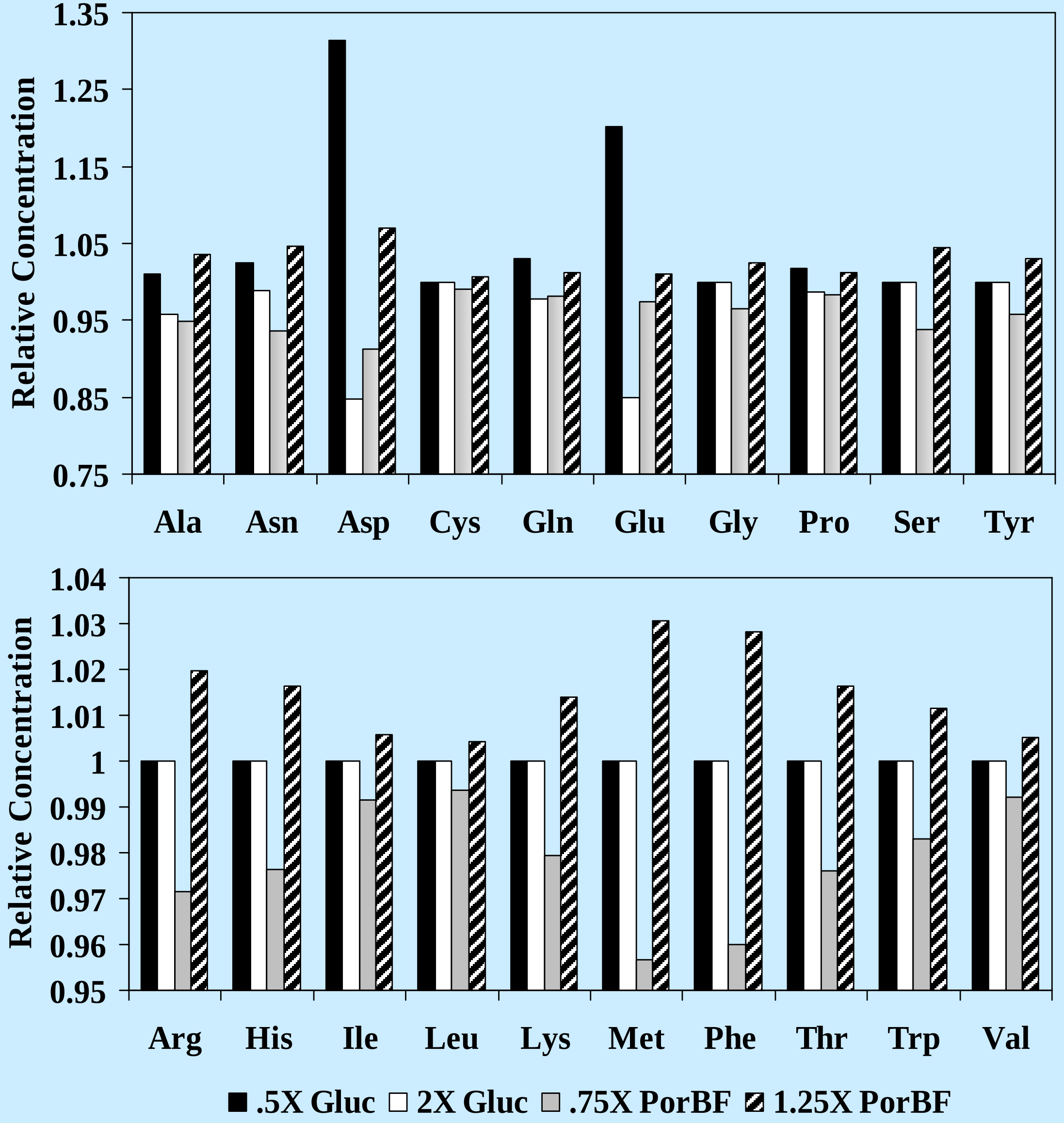
Hanigan et al. (2004)



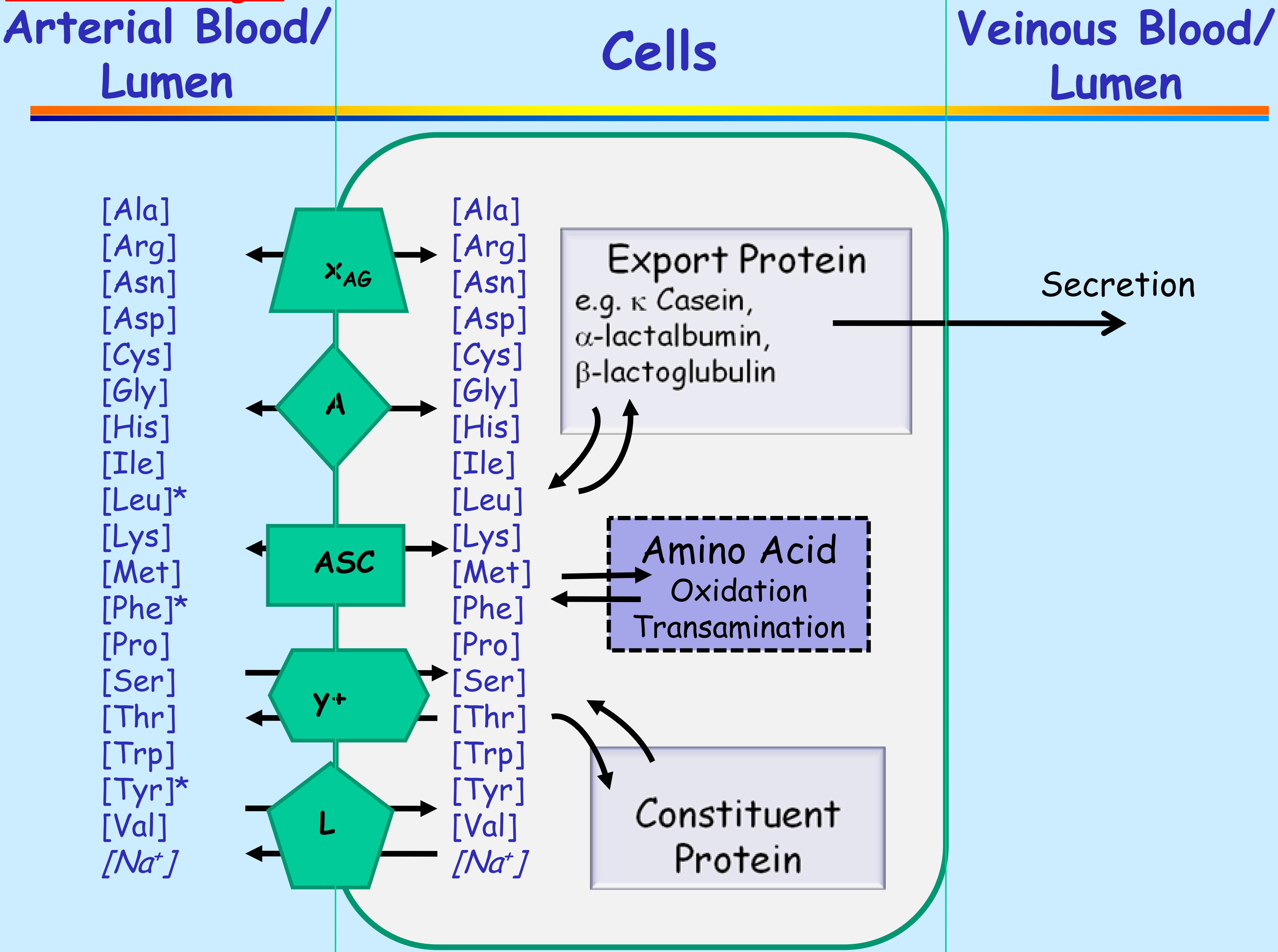
Flow diagram



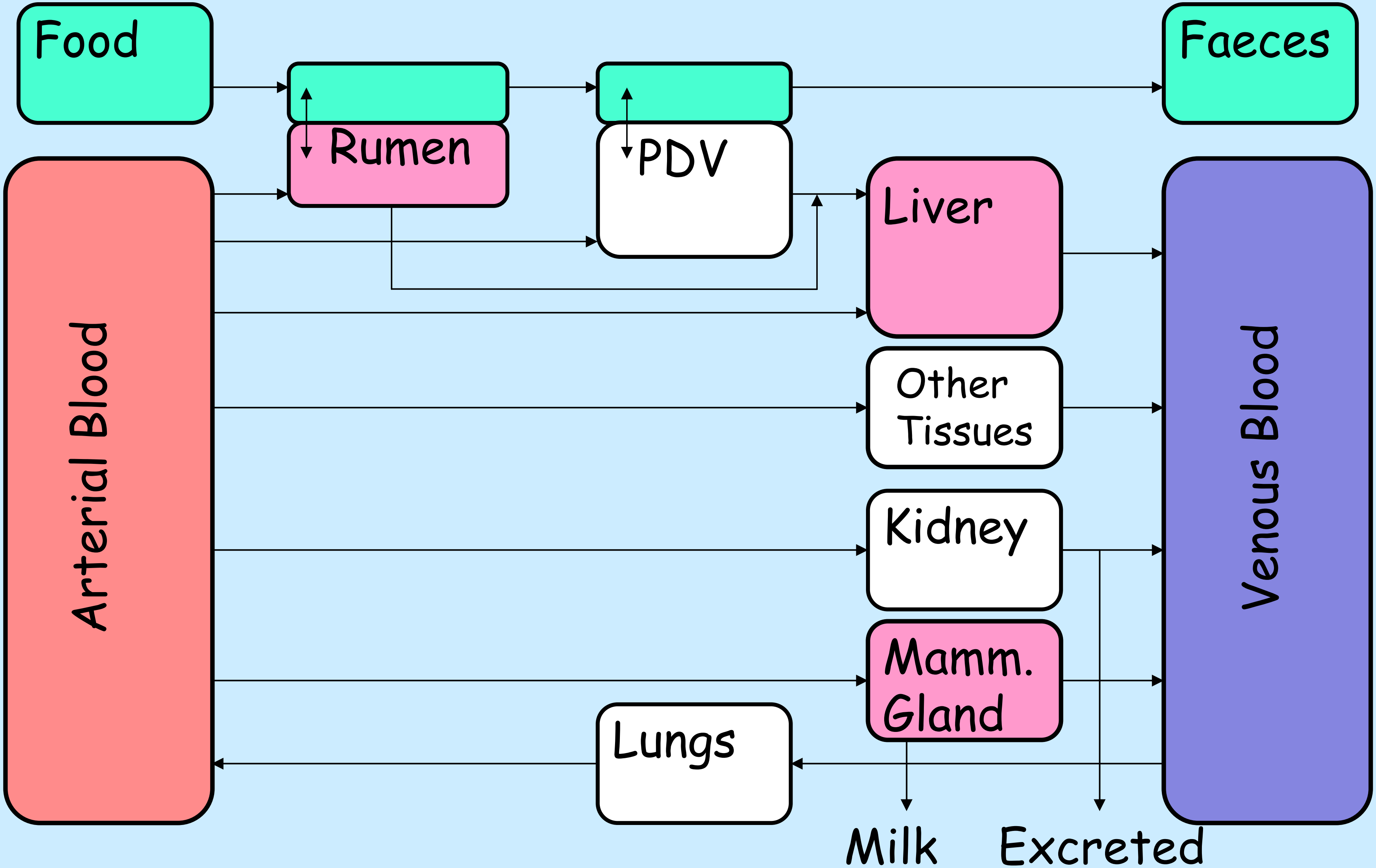
Application



Future challenges



Integrative model of whole-body N metabolism



Major challenges

- Fluxes for only a limited number of AA have been quantified using isotopes (LEU, PHE/TYR)
- Virtually no data measured with isotopes on AA metabolism in response to changes in energy supply
- Various questions remain on non-linearity of response in AA metabolism to variation in AA concentrations
- No process-based simulation models of the gut
- Co-ordination of nutrient supply to various organs and tissues (blood flow; hormonal influences) within an integrative simulation model needs to be addressed
- Some good stuff out there, but modelling intermediary N metabolism in dairy cows remains a work-in-progress

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Innovation and practical management approaches to reduce nitrogen excretion by ruminants

Application