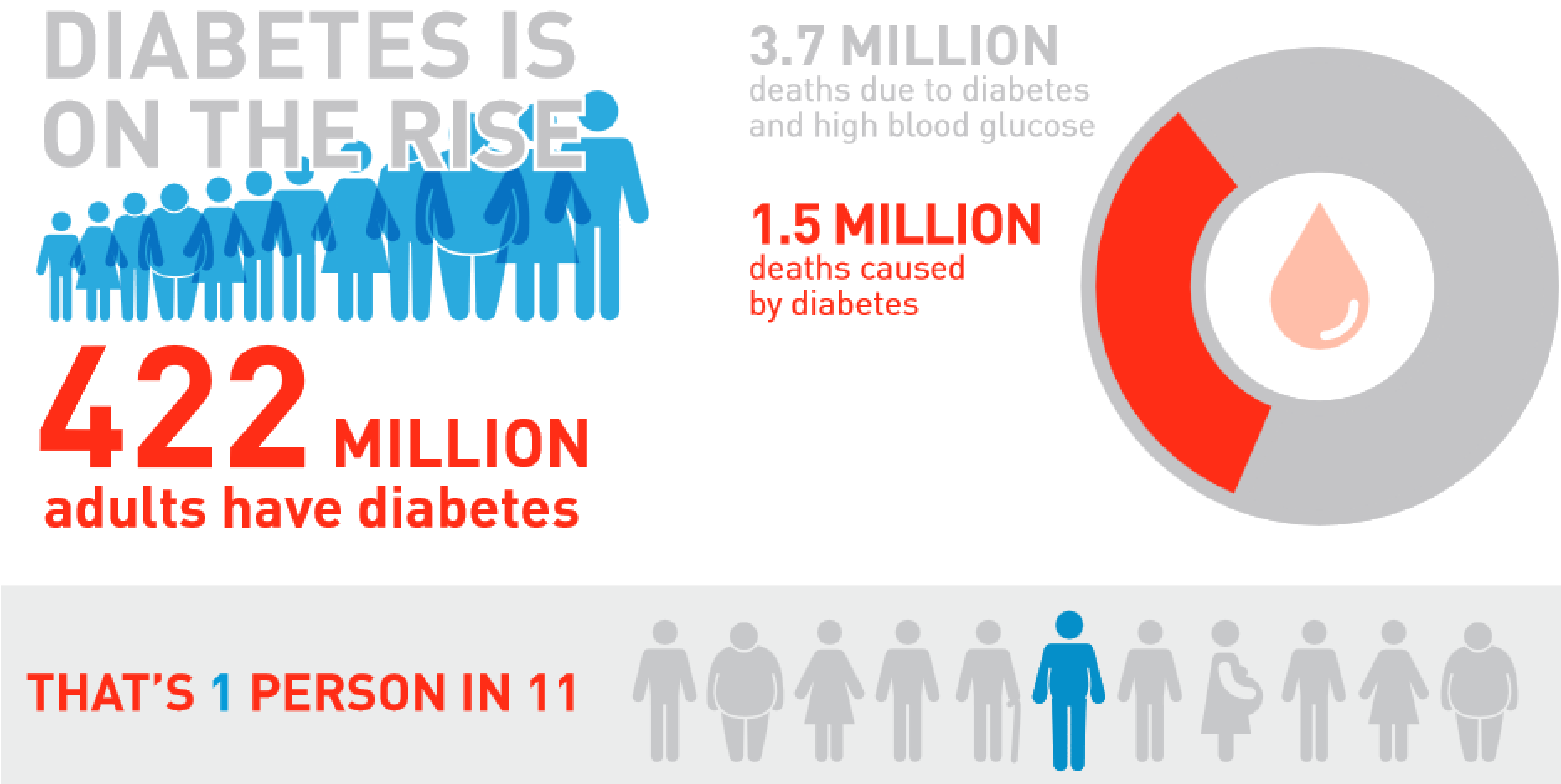
Technische
Universität
Braunschweig

Analysing Metabolic Pathways with Stable Isotope Labeling

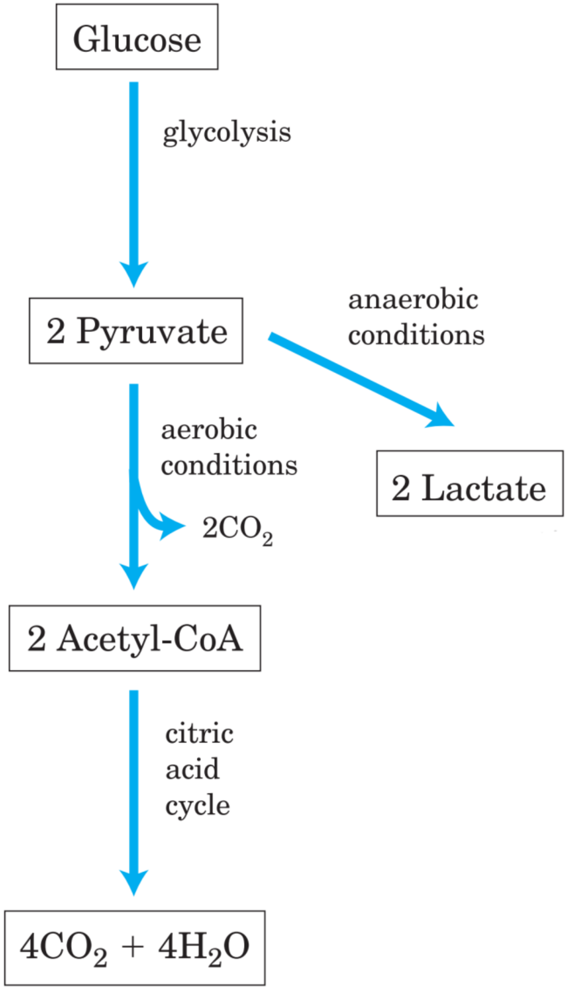
Martin Zembaty | 17.1.2017

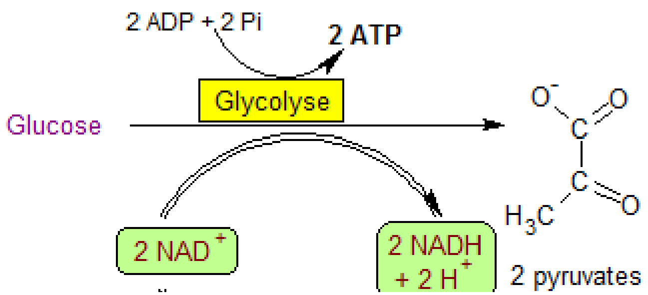
Diabetes



Source: World Health Organization

Fate of pyruvate (aerobic / anaerobic)





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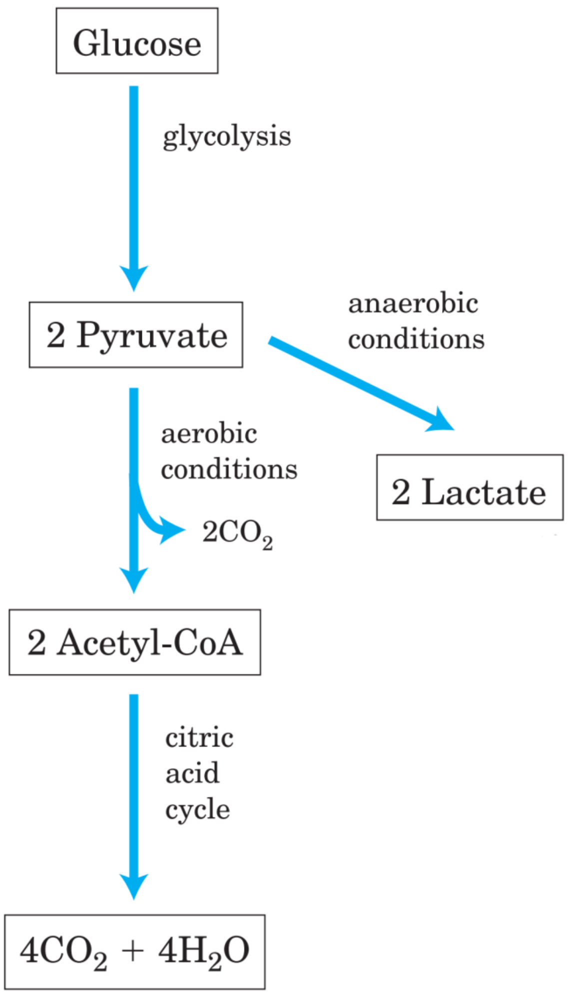
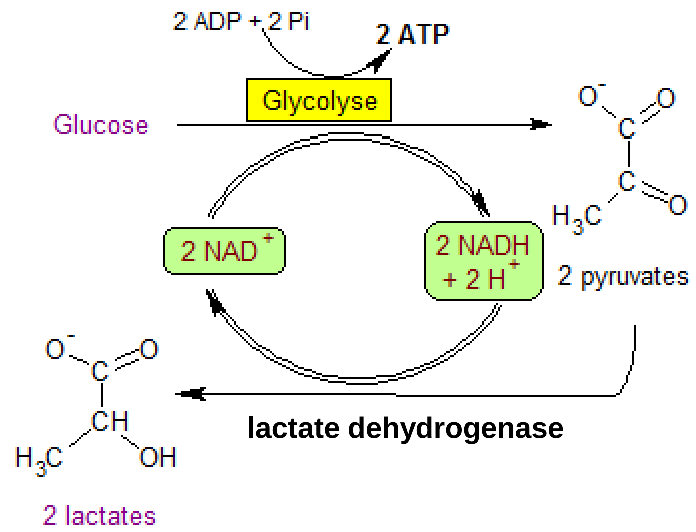
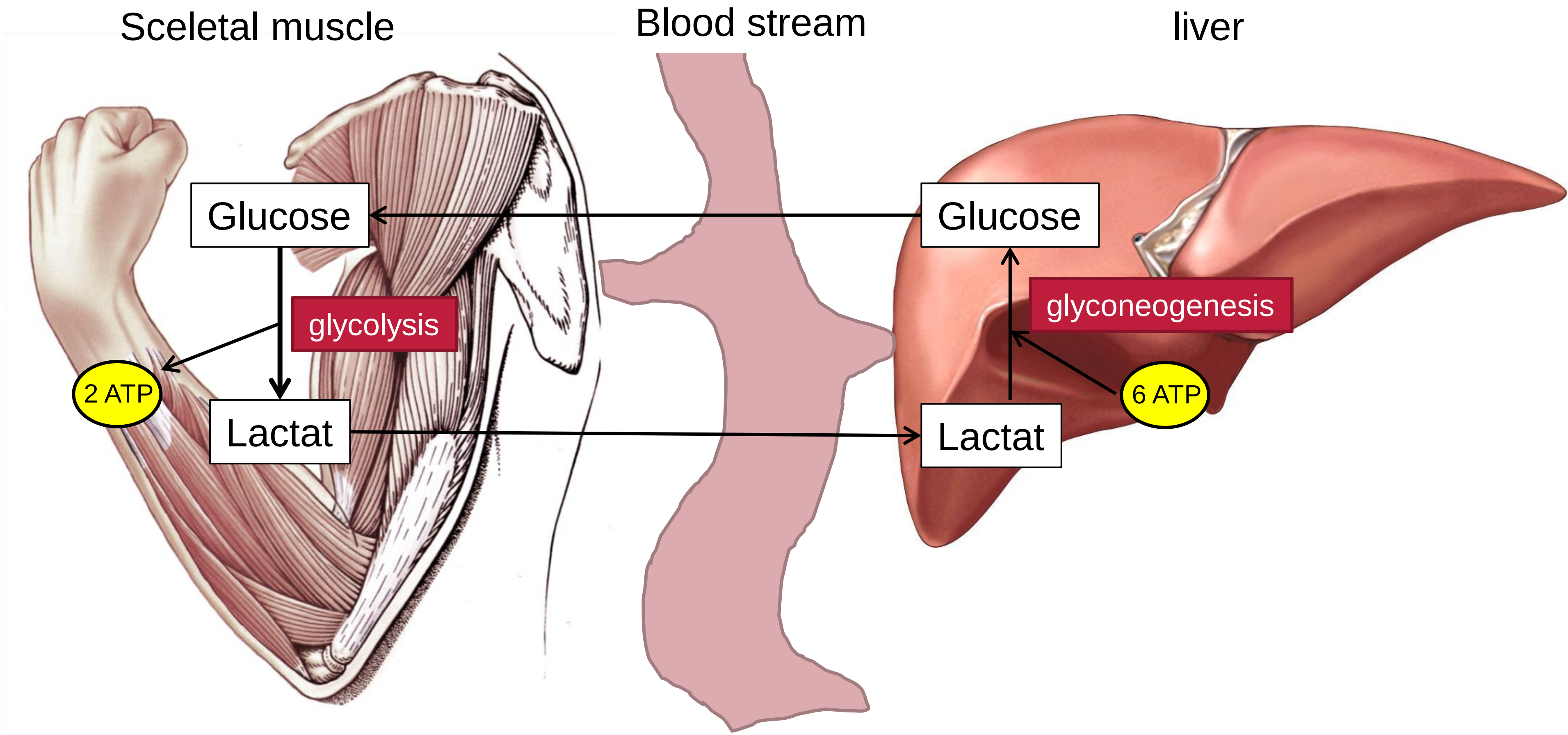




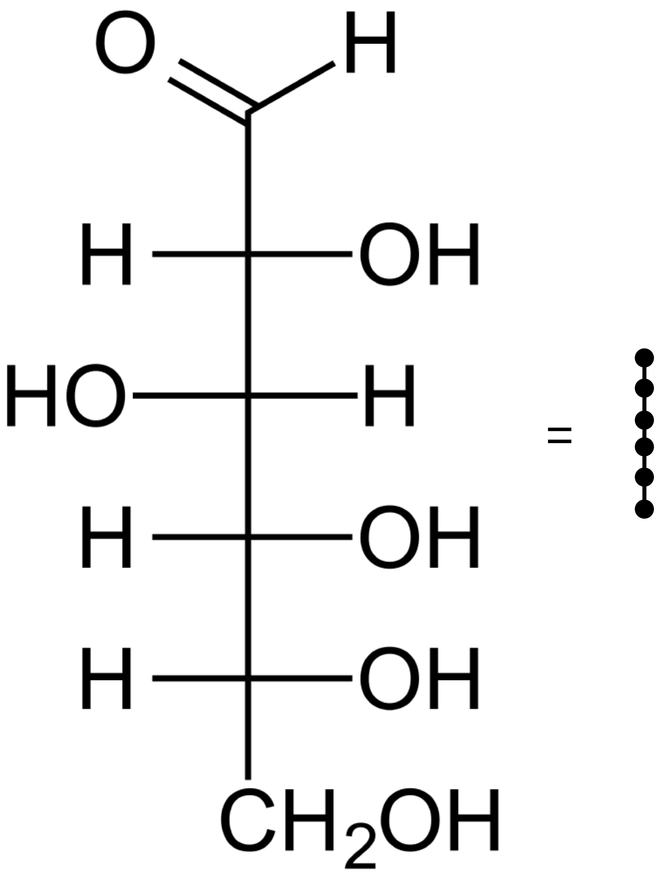
Cori Cycle



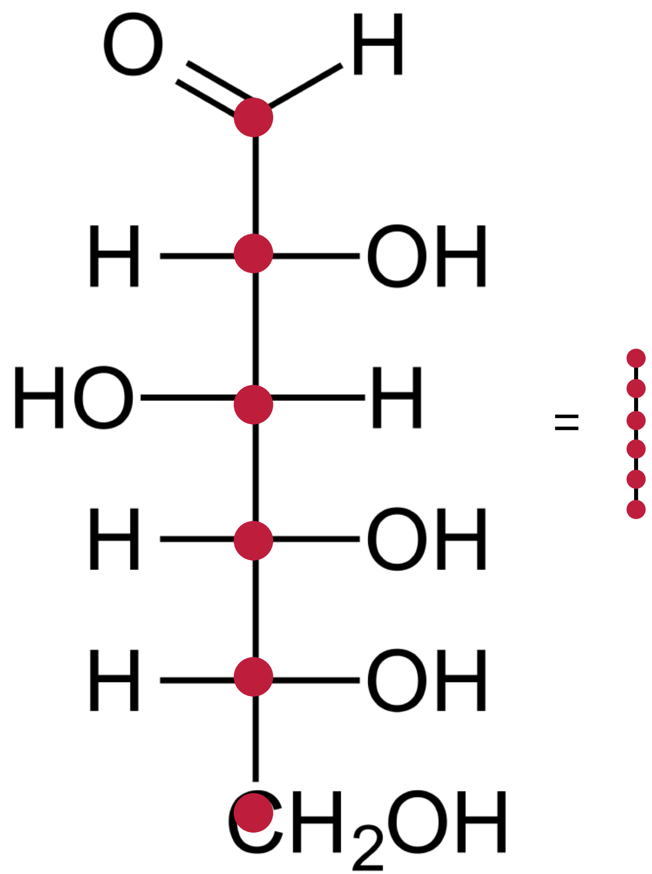
Source: Studyblue.com

Source: pcosnutrition.com

Stable isotope labeling



D-Glucose

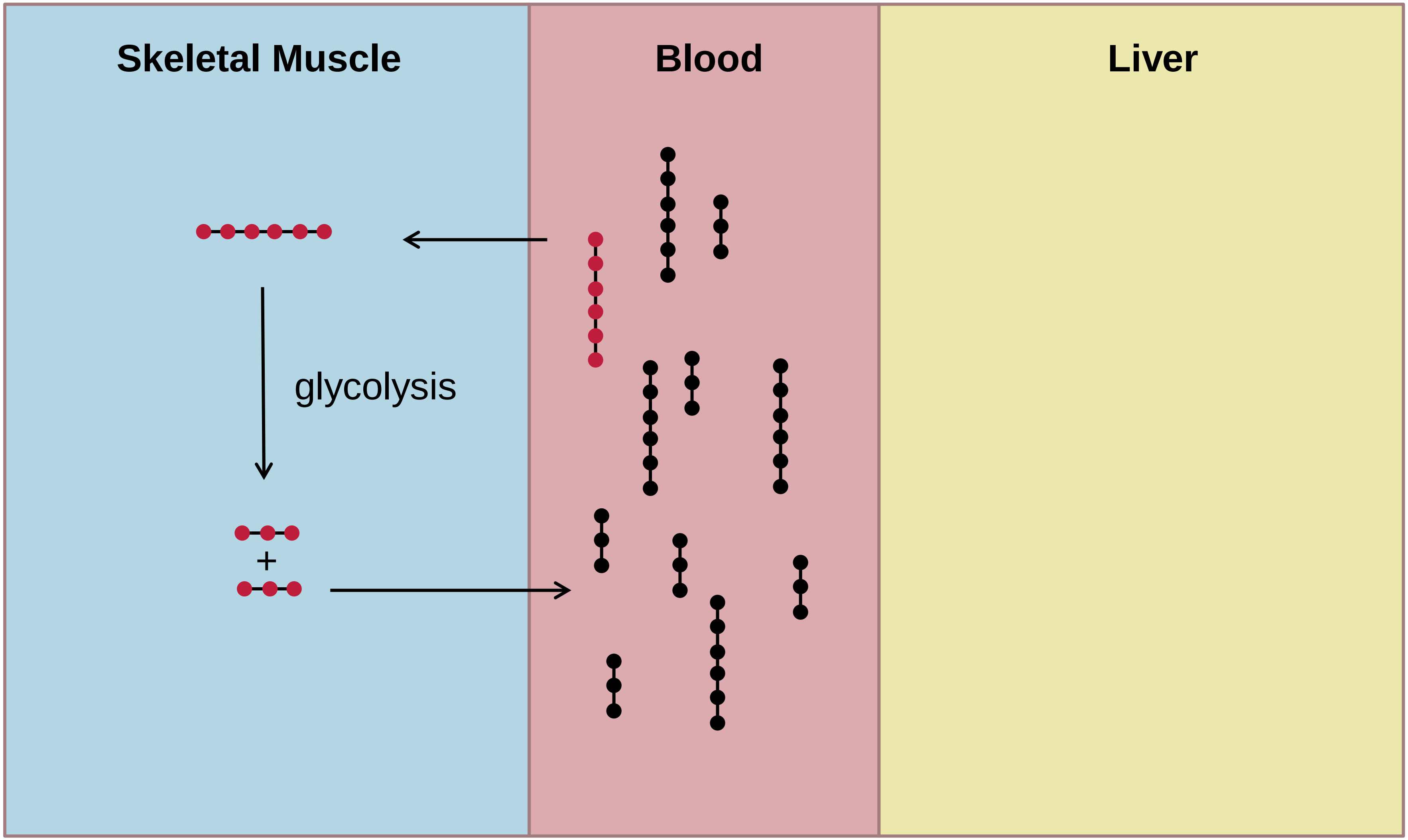


$[U^{13}C_6]$-Glucose

Getting stable isotopes into the system

Source: virginpure.com

Tracking Cori Cycle activity with stable isotope labeling



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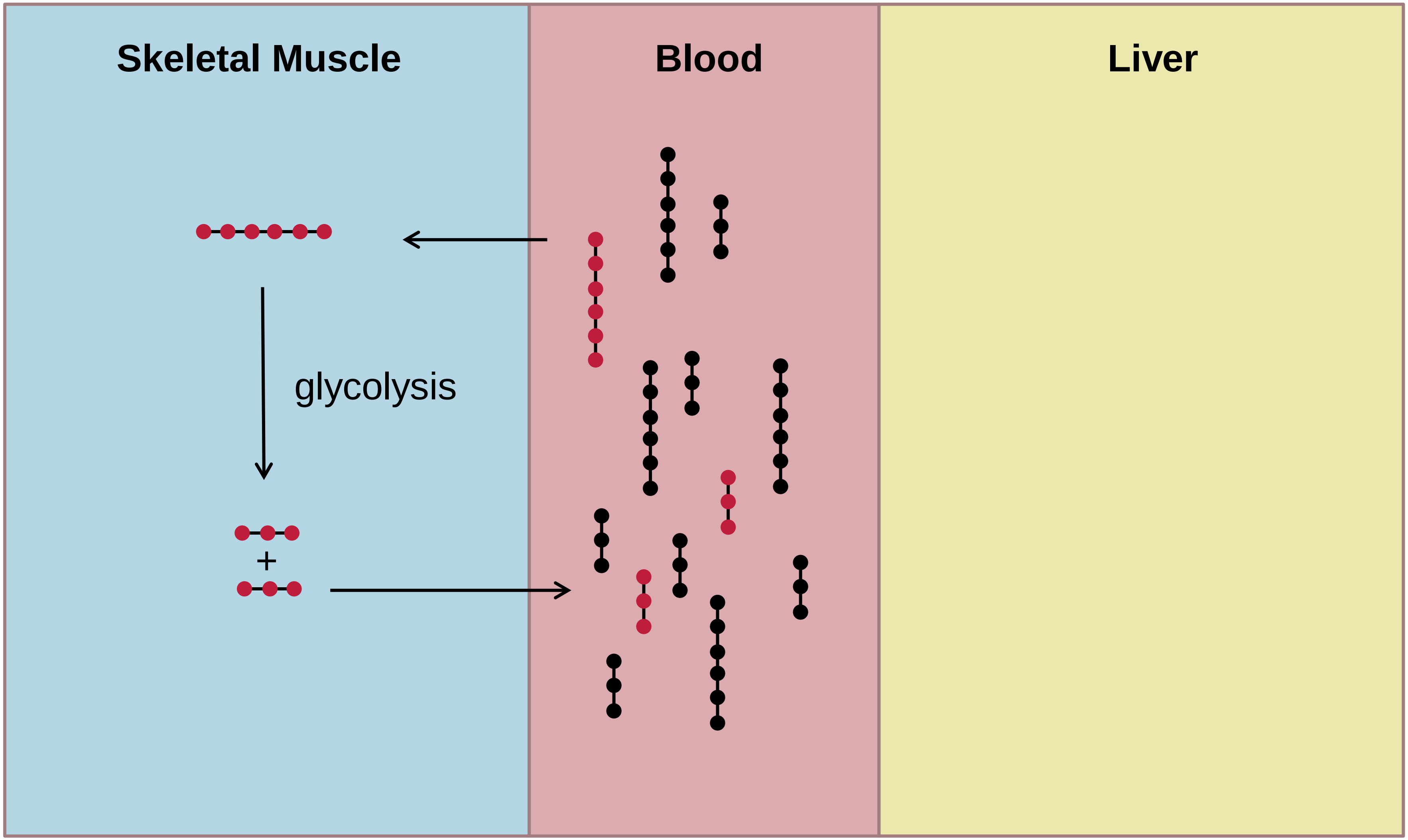
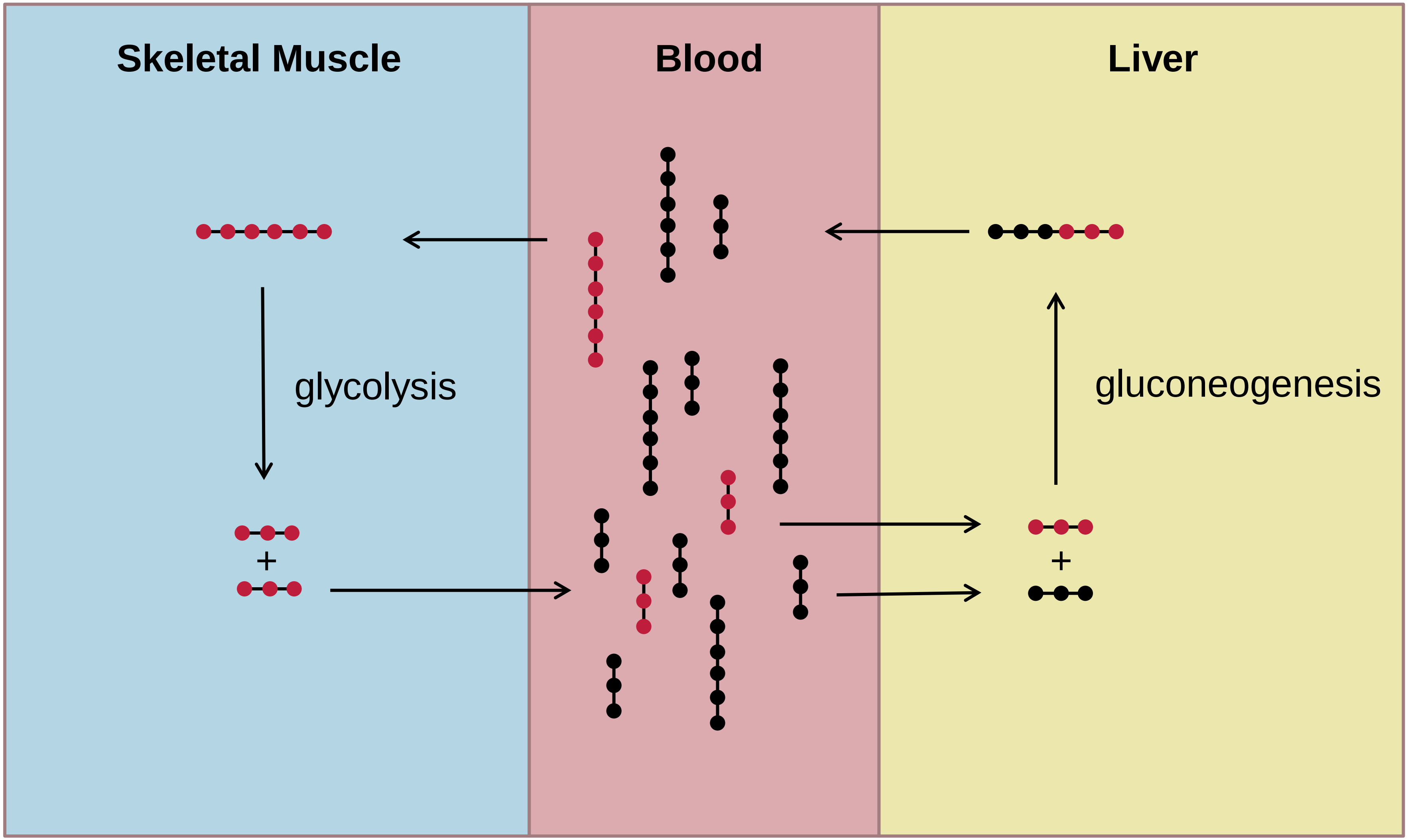
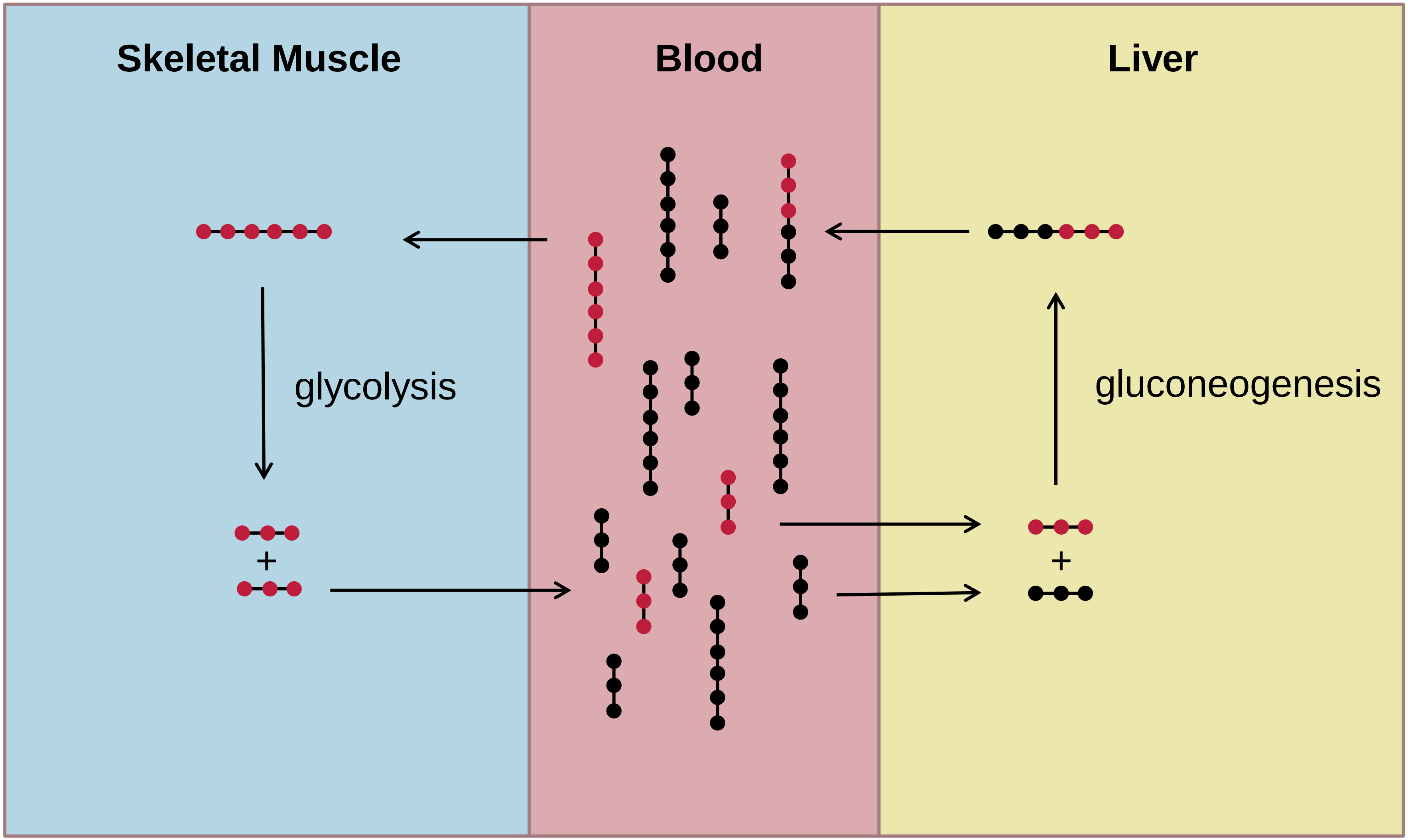


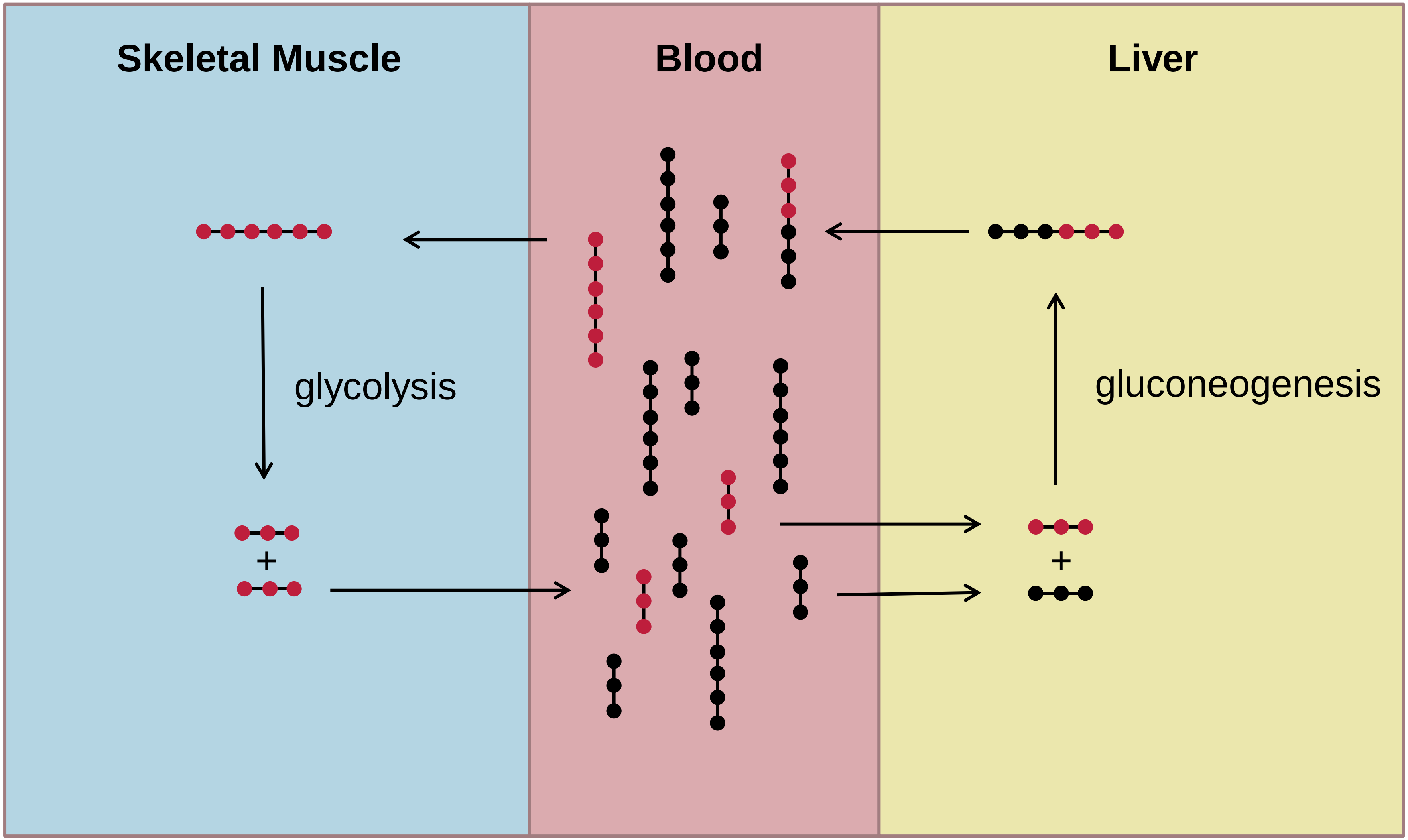
Tracking Cori Cycle activity with stable isotope labeling



Tracking Cori Cycle activity with stable isotope labeling



Tracking Cori Cycle activity with stable isotope labeling

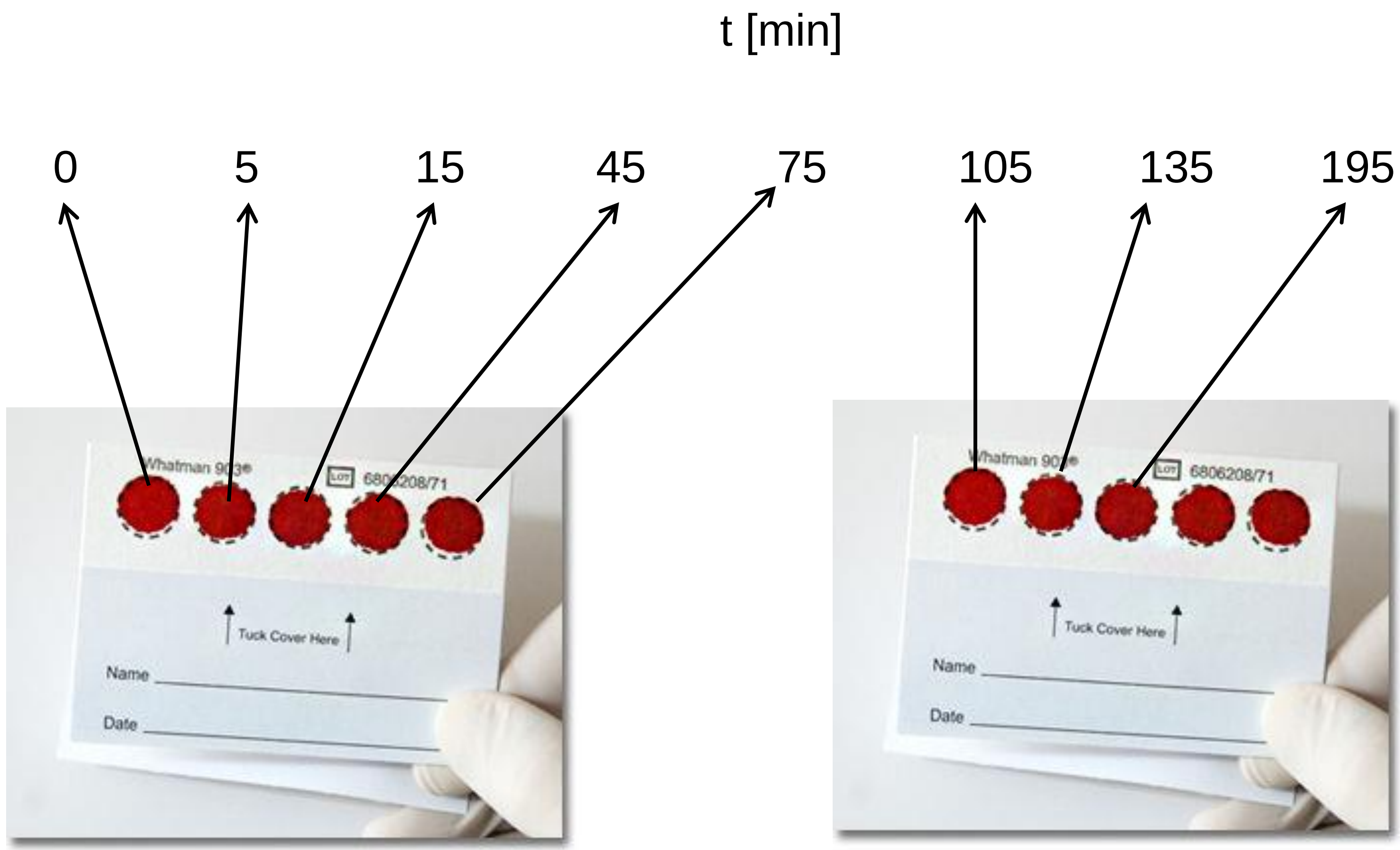


The Sampling Kit

Source: Karsten Hiller

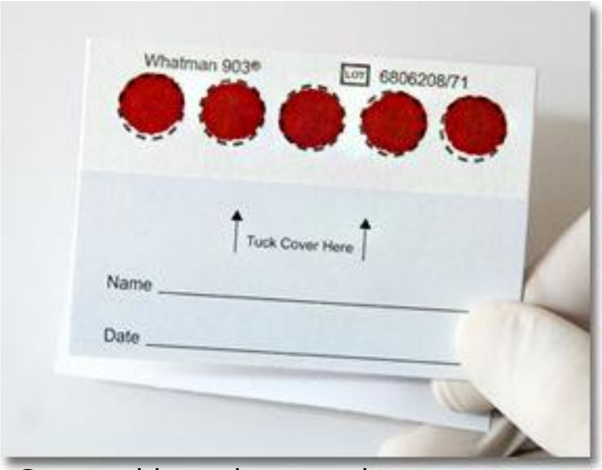
Dried blood spots

Blood samples



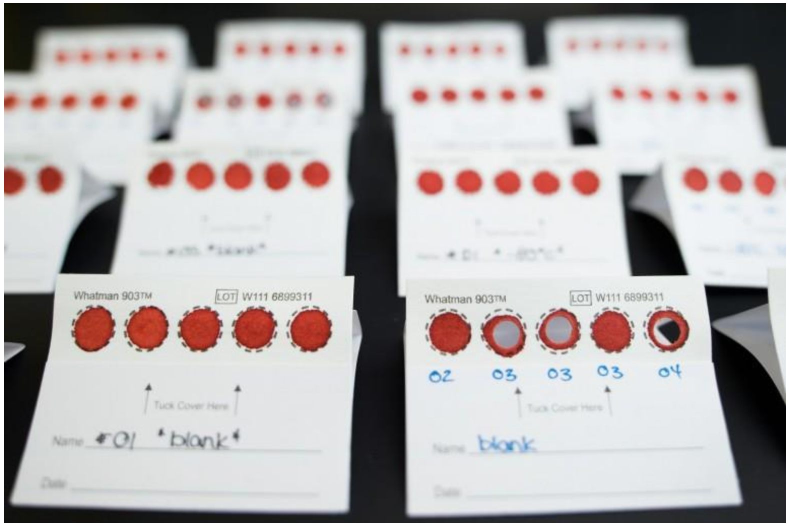
Dried blood spots

Source: Vitas.no



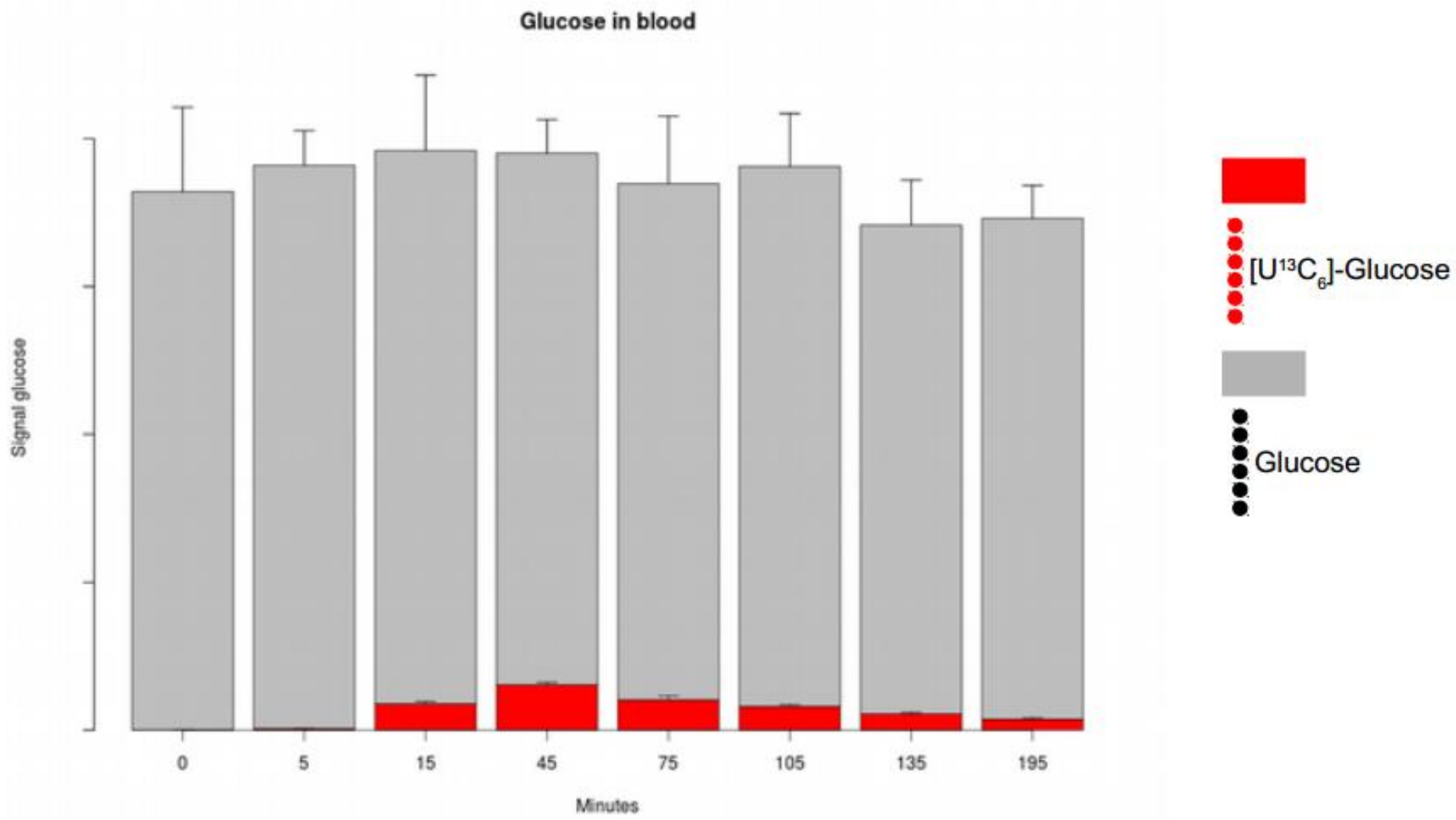
Source: biomerieux.co.uk

Source: technologyreview.com

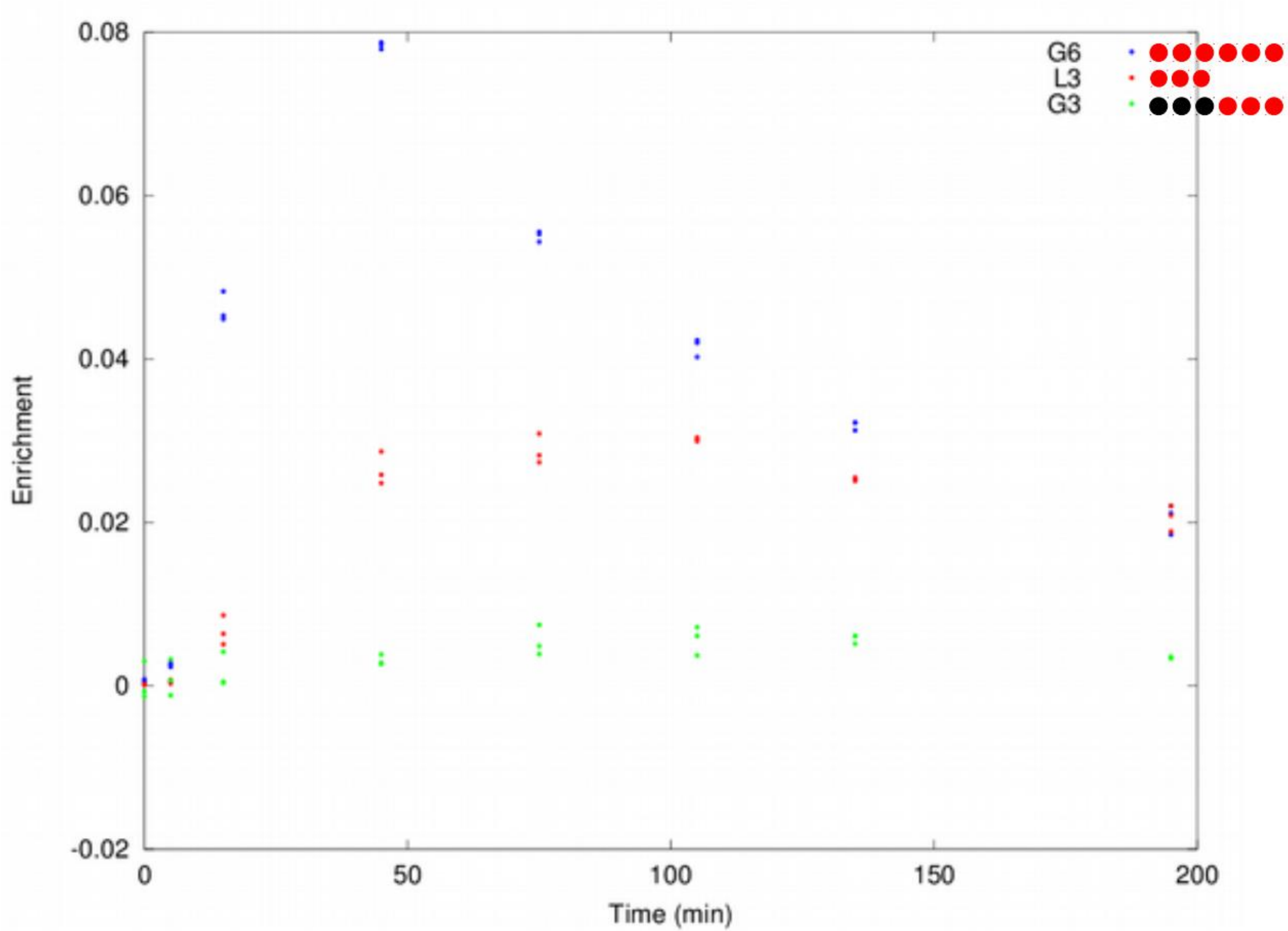


Source: gizmag.com

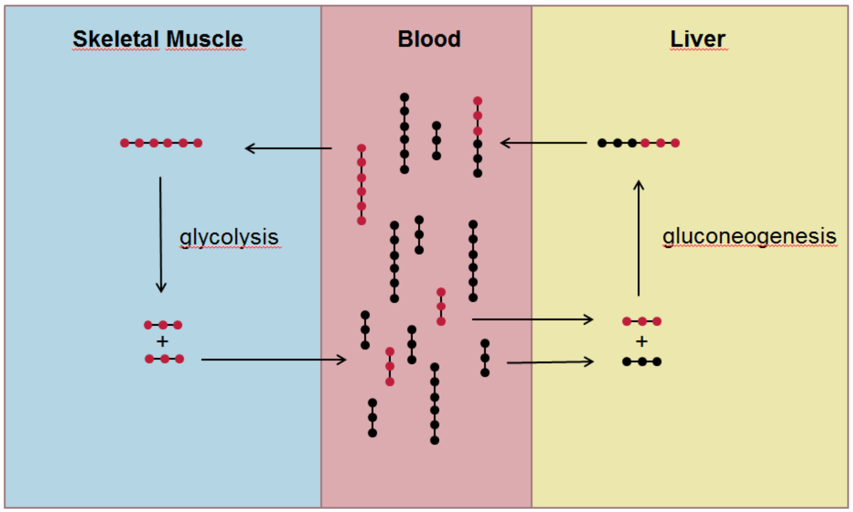
Stable isotopes display the dynamics

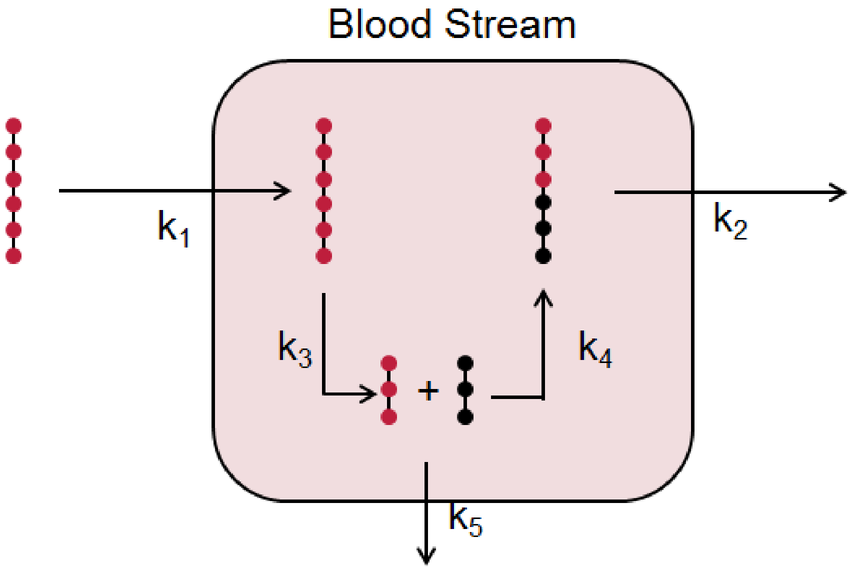


Data from healthy patients

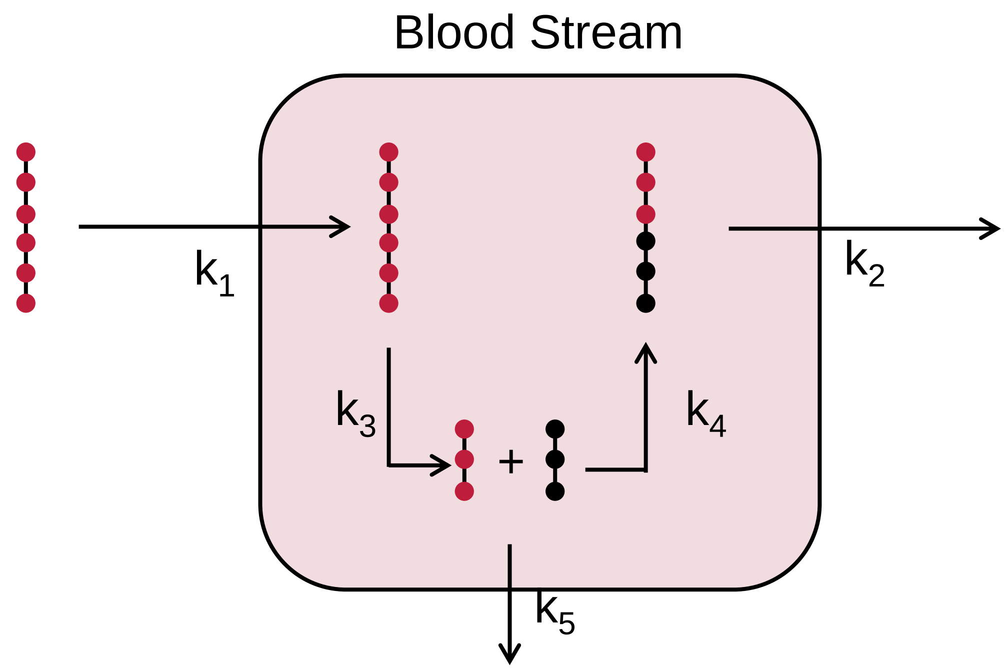


Tracking Cori Cycle activity with stable isotope labeling

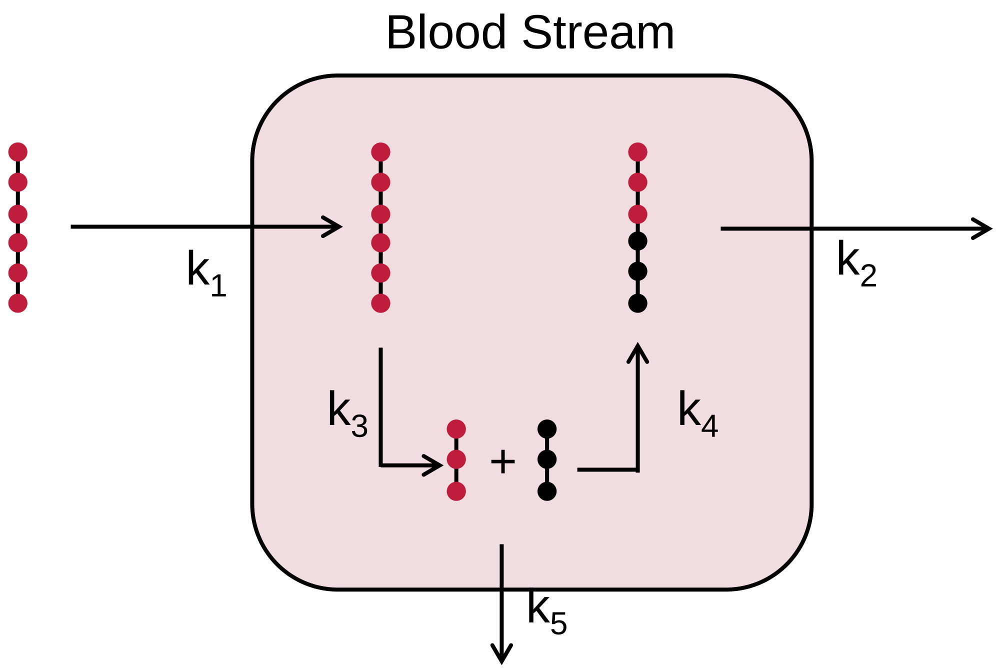




Modeling the Cori Cycle with Differential equation system



Modeling the Cori Cycle with Differential equation system



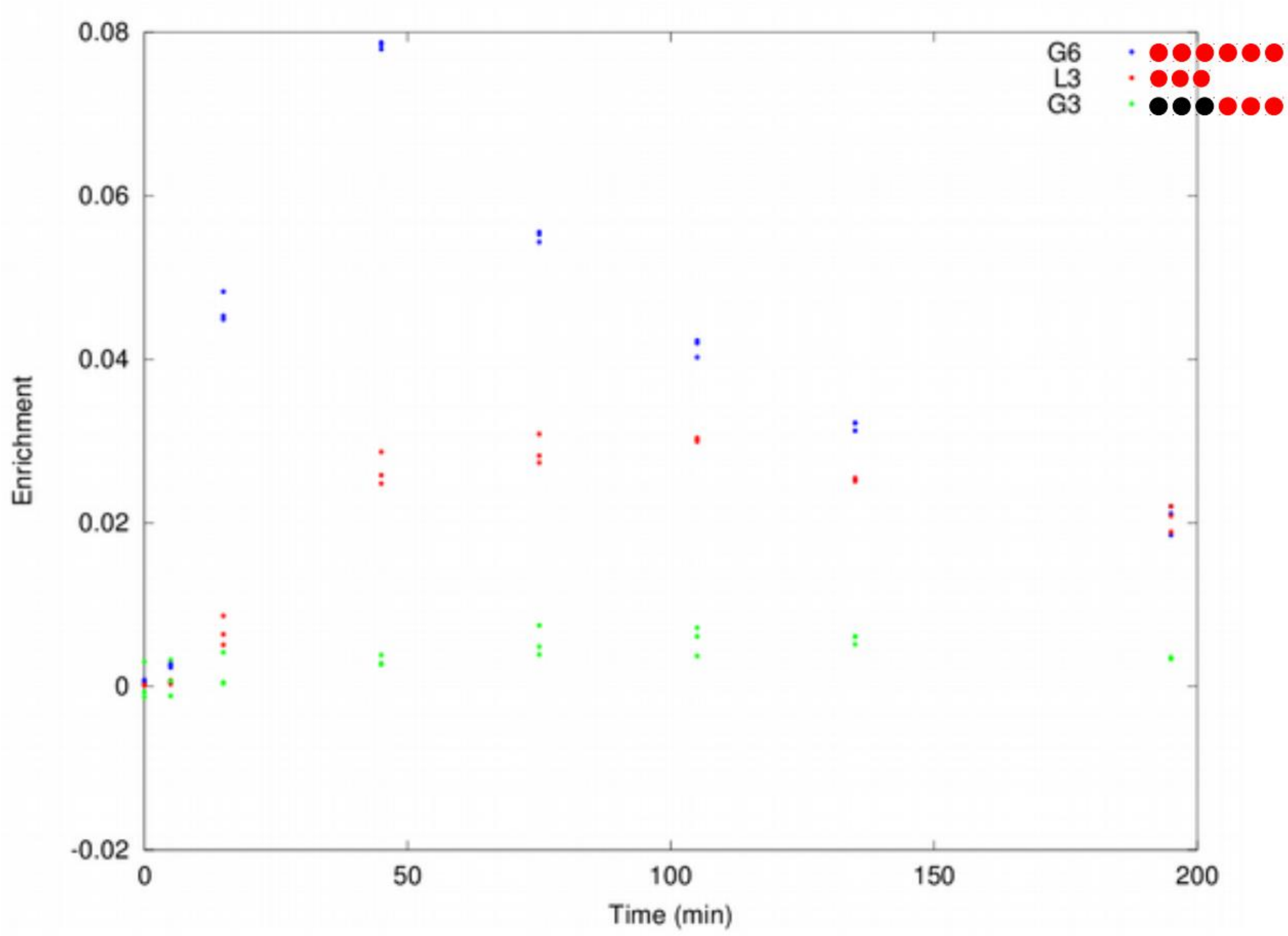
$$\frac{dG6_i}{dt} = -k1 \cdot G6_i(t)$$

$$\frac{dG6_i}{dt} = -k1 \cdot G6_i(t) - k2 \cdot G6_b(t) - k3 \cdot G6_b(t)$$

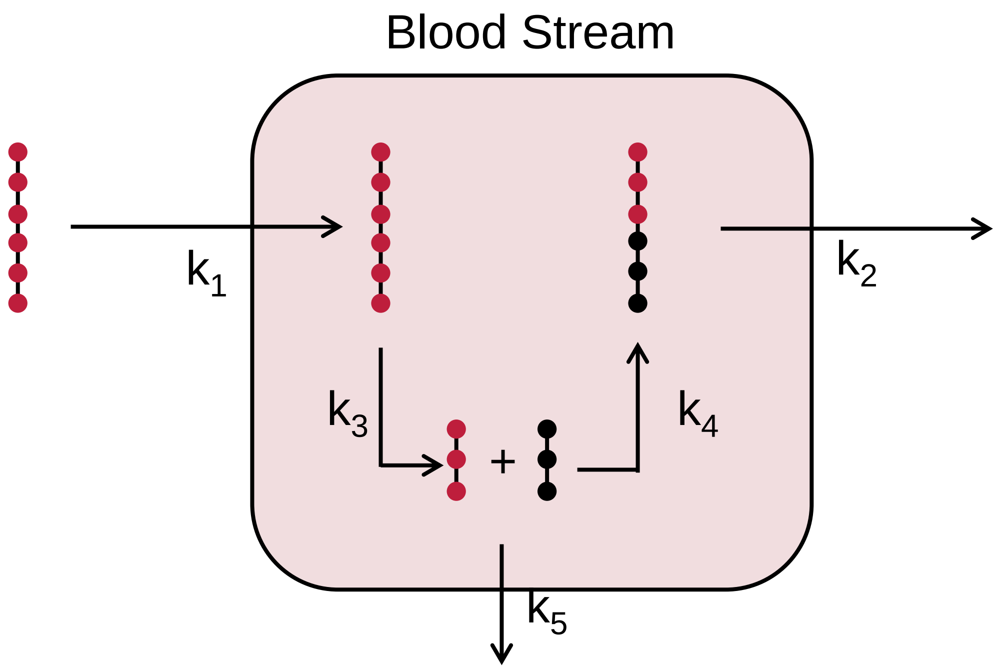
$$\frac{dL3_i}{dt} = k_3 \cdot G6_b(t) - k_4 \cdot L3(t) - k_5 \cdot L3(t)$$

$$\frac{dG3}{dt} = k_4 \cdot L3(t) - k_2 \cdot G3(t) - k_3 \cdot G3(t)$$

Data from healthy patients



Fitting the model



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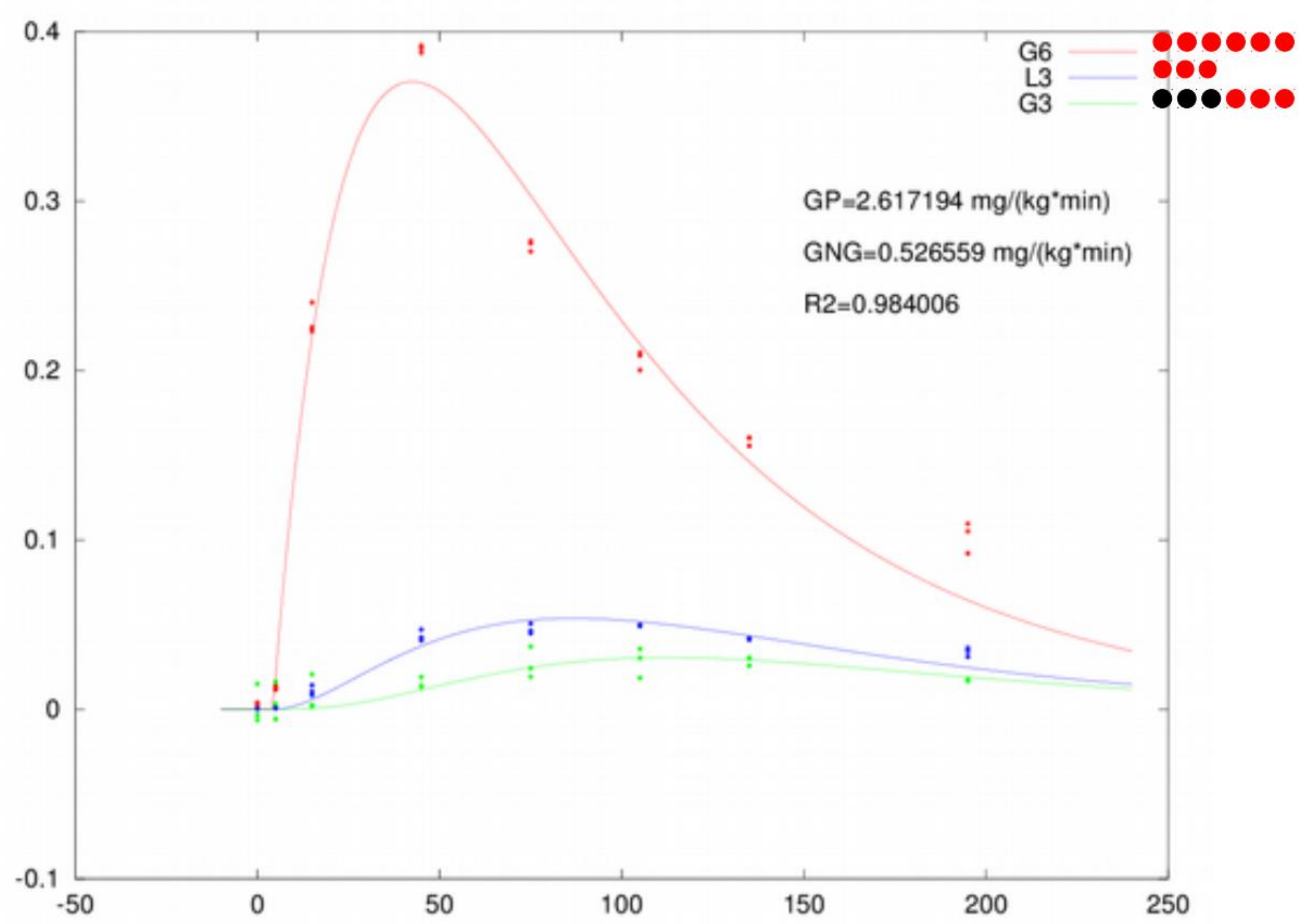
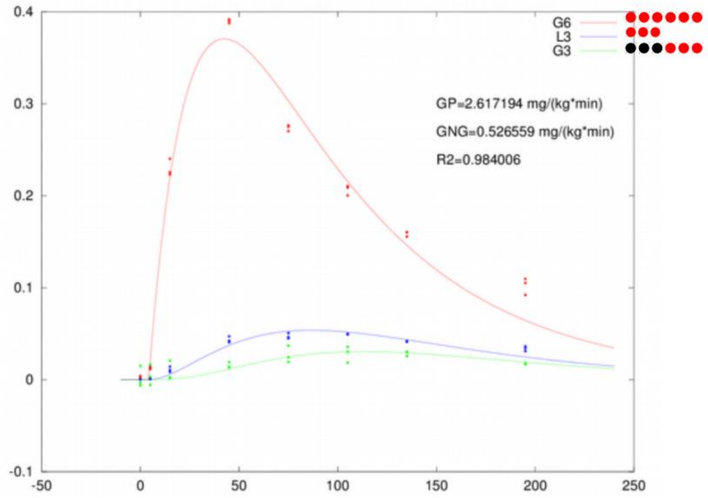
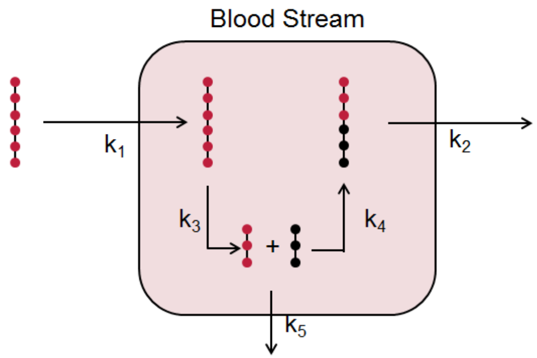
Fitting the model

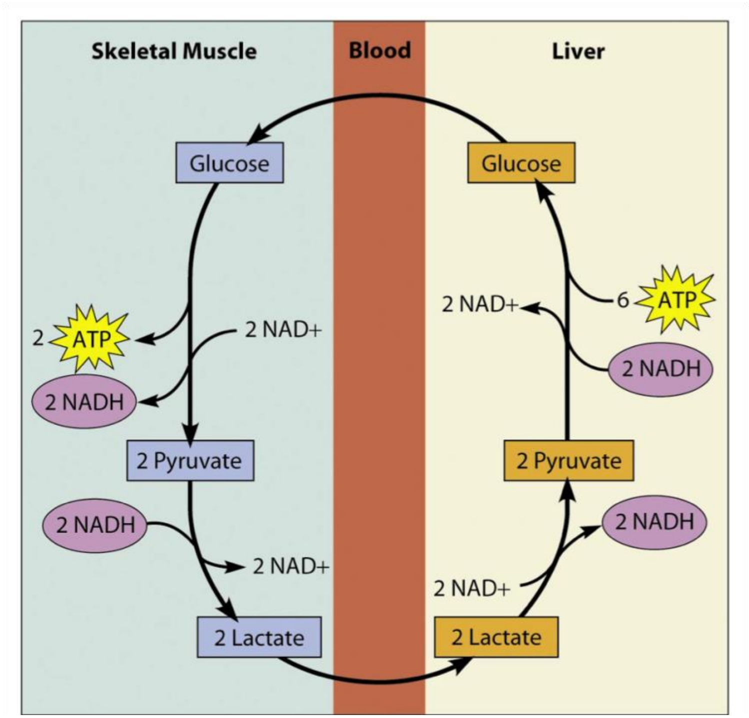


I have a working model now. What can I do with it?

Calculating flows just by analysing DBS







Further investigations with unhealthy patients

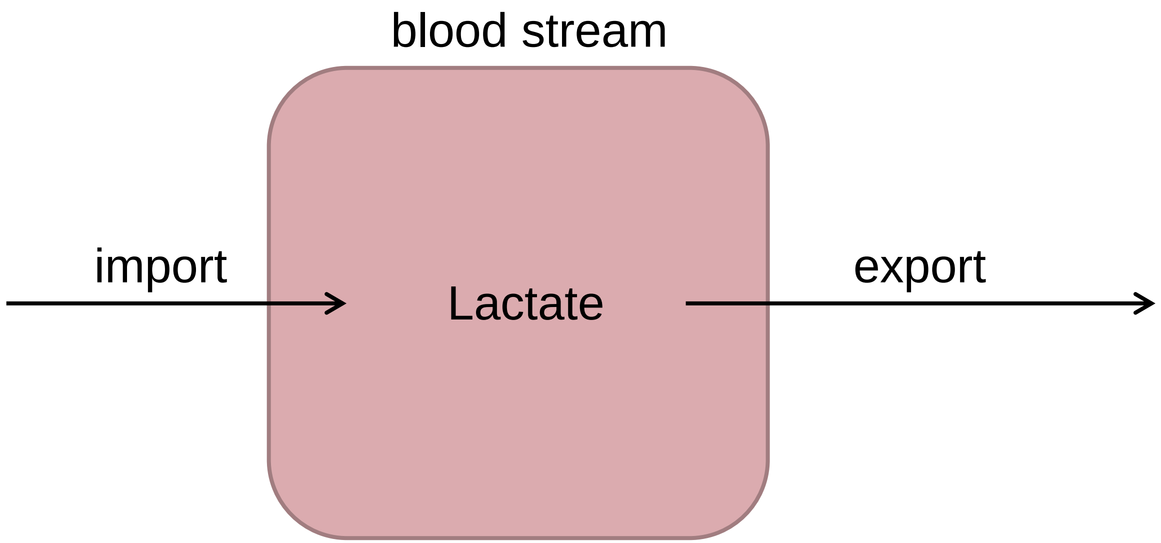
Take home message

- Stable Isotope Labeling can be used to analyse metabolic pathways in vivo

- There are 3 major steps:
  - Developing a method to introduce the labled metabolites into your system & sampling them
  - Creating a model
  - Fitting the model with data from your experiments

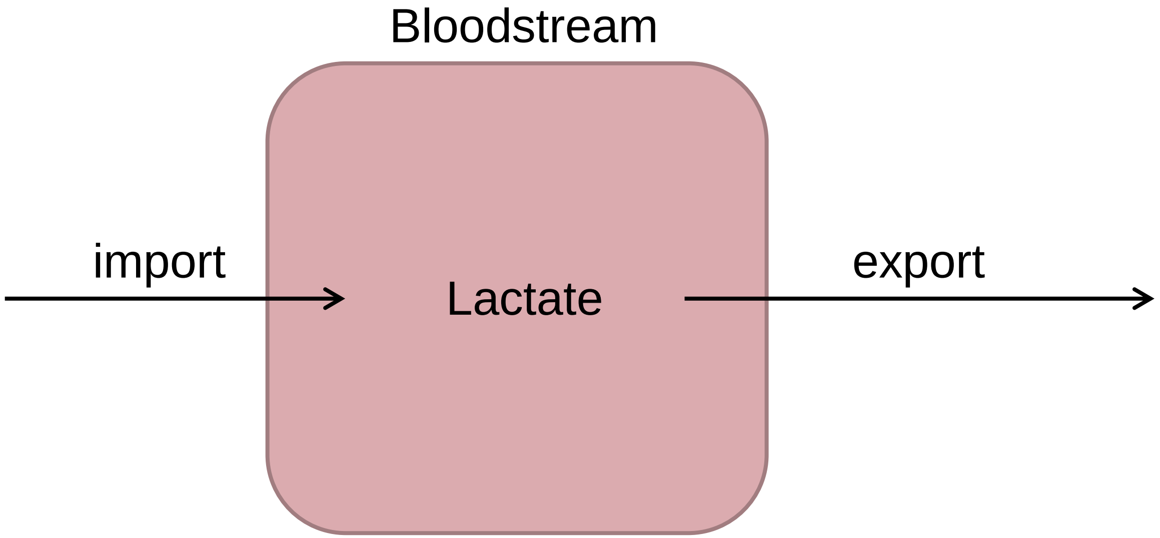
Thank your for your attention!

Ordinary Differential Equations



$Rate_{import}(t)$ $BS(t)$ $Rate_{export}(t)$

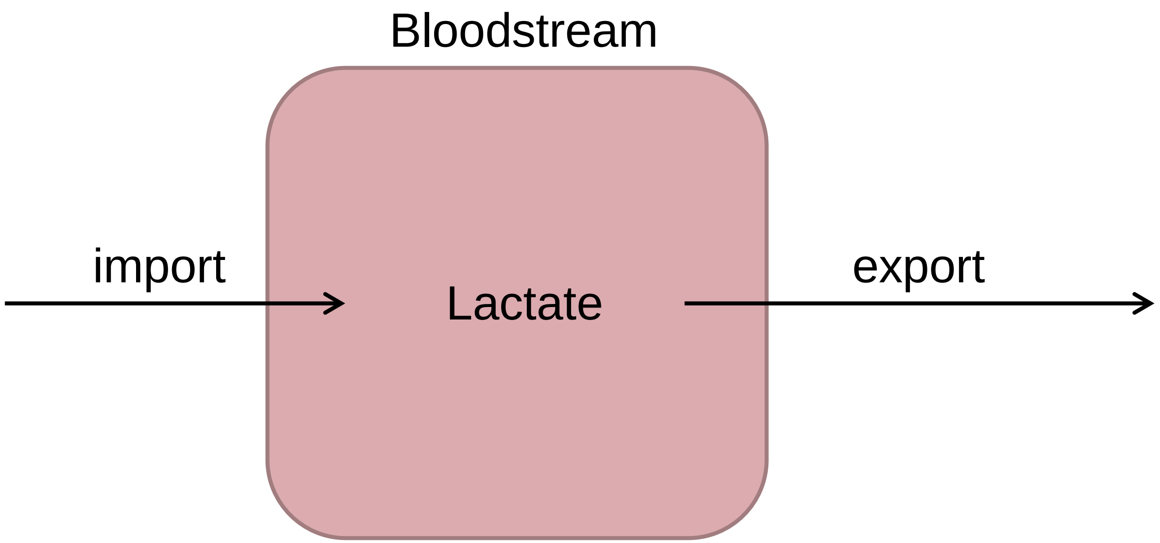
Ordinary Differential Equations



$Rate_{import}(t)$ BS(t) $Rate_{export}(t)$

$$BS(t+\Delta t) = BS(t) + Rateimport(t) * \Delta t - Rateexport(t) * \Delta t$$

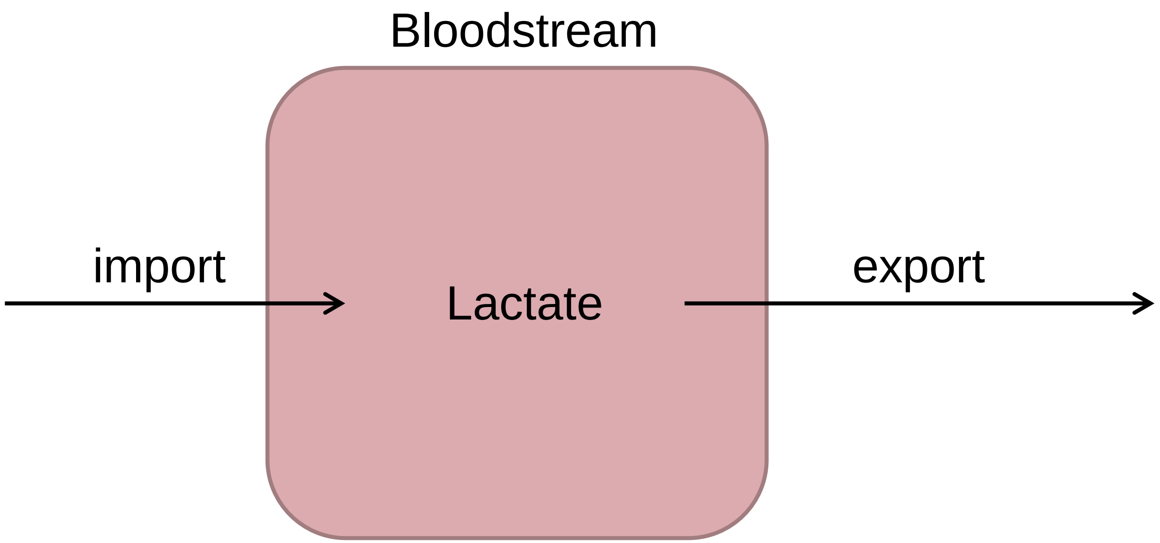
Ordinary Differential Equations



$$BS(t+\Delta t) = BS(t) + Rateimport(t) * \Delta t - Rateexport(t) * \Delta t$$

$$\frac{BS(t+\Delta t) - BS(t)}{\Delta t} = Rate_{import}(t) - Ratee_{xport}(t)$$

Ordinary Differential Equations



$$\frac{BS(t+\Delta t)-BS(t)}{\Delta t} = Rate_{import}(t) - Ratee_{xport}(t)$$

$$\frac{dBS(t)}{dt} = Rate_{import}(t) - Ratee_{xport}(t)$$

$$\frac{dBS(t)}{dt} =$$ derivative of the amount of Lactate

Ordinary Differential Equations

$$\frac{dBS(t)}{dt} = Rate_{import}(t) - Rateex_{port}(t)$$

General form of the ODE

$$\frac{dx}{dt} = \sum Rates_{production} - \sum Rates_{loss}$$

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