First steps into the dynamical modelling and gene regulatory network reconstruction of the trypanosome parasite response in mice

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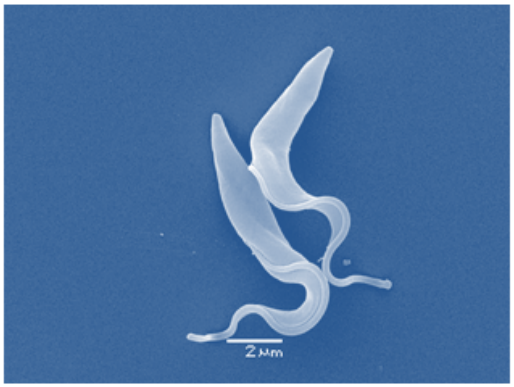
Introduction

- Trypanosomes and their infection dynamics.
- Existing experimental setup and data—
  - gene expression/metabolite profiles over course of infection.
- Preparation of expression profiles for dynamical modelling—
  - pseudotemporal ordering.
- Proposal for dynamical modelling study.

Trypanosomes

- Trypanosomes are a parasite that cause a number of diseases in various animals.
- Notably *sleeping sickness* in humans and cattle, which causes around 8000 human deaths per year and >20 million ($2.5 billion) cattle infections in sub-Saharan Africa.
- Cell membrane has a Variable Surface Glycoprotein coat that evades the immune system:
  - VSG coats the membrane blocking antigens,
  - also undergoes frequent stochastic genetic modification rendering previous antigens useless.

Host-parasite genotype infection matrix

BALB/c	C57Bl/6
	
Susceptible	Tolerant
	
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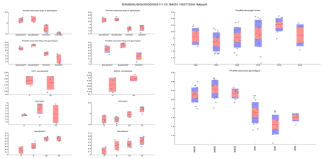
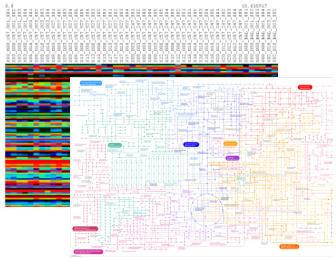
Experimental workflow setup

Total RNA from 89 mouse spleen samples covering all treatments for transcriptome analysis

RNA sequencing (Edinburgh Genomics)



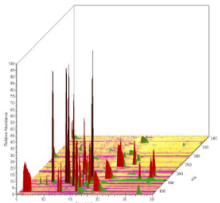
Differential gene expression analysis to identify differences within species and across species



Mapping transcriptome on to metabolome

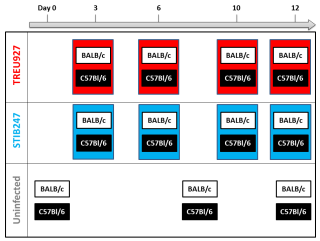
Plasma from the same 89 mouse samples used for metabolome analysis

Metabolite data (University of Glasgow)

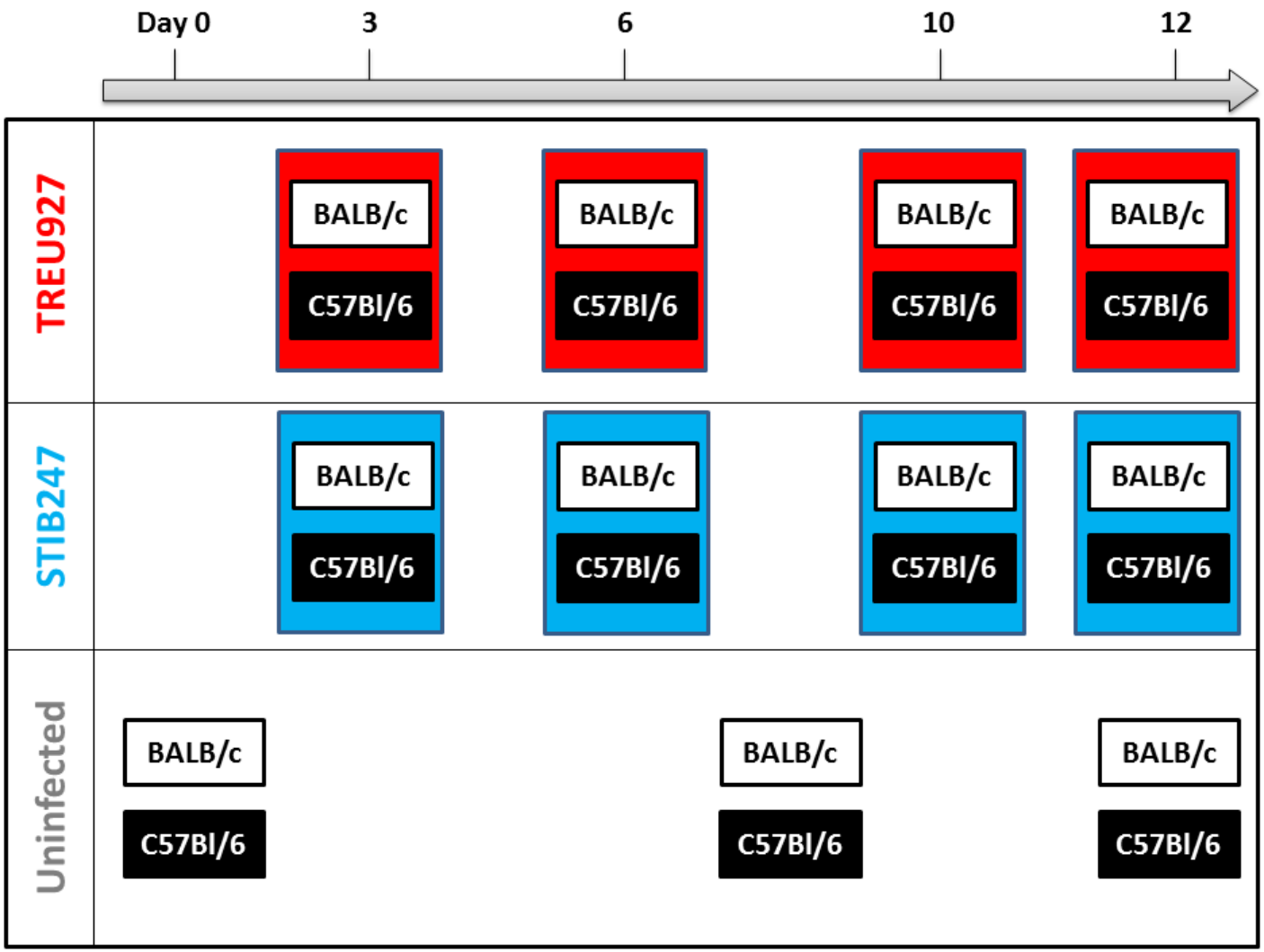


Analysis and annotation of metabolite data

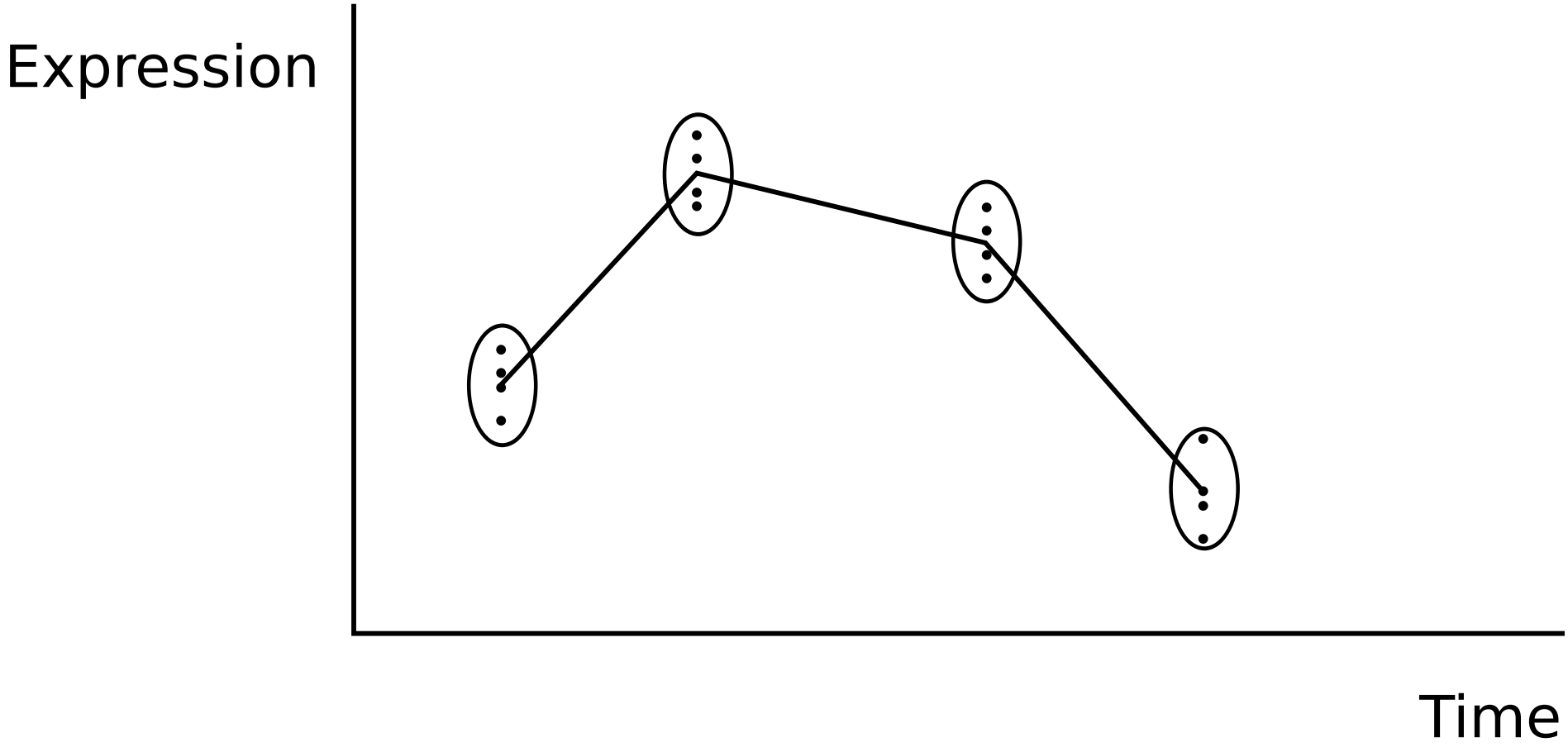
Time series for systemic host-parasite response



Experimental time series setup



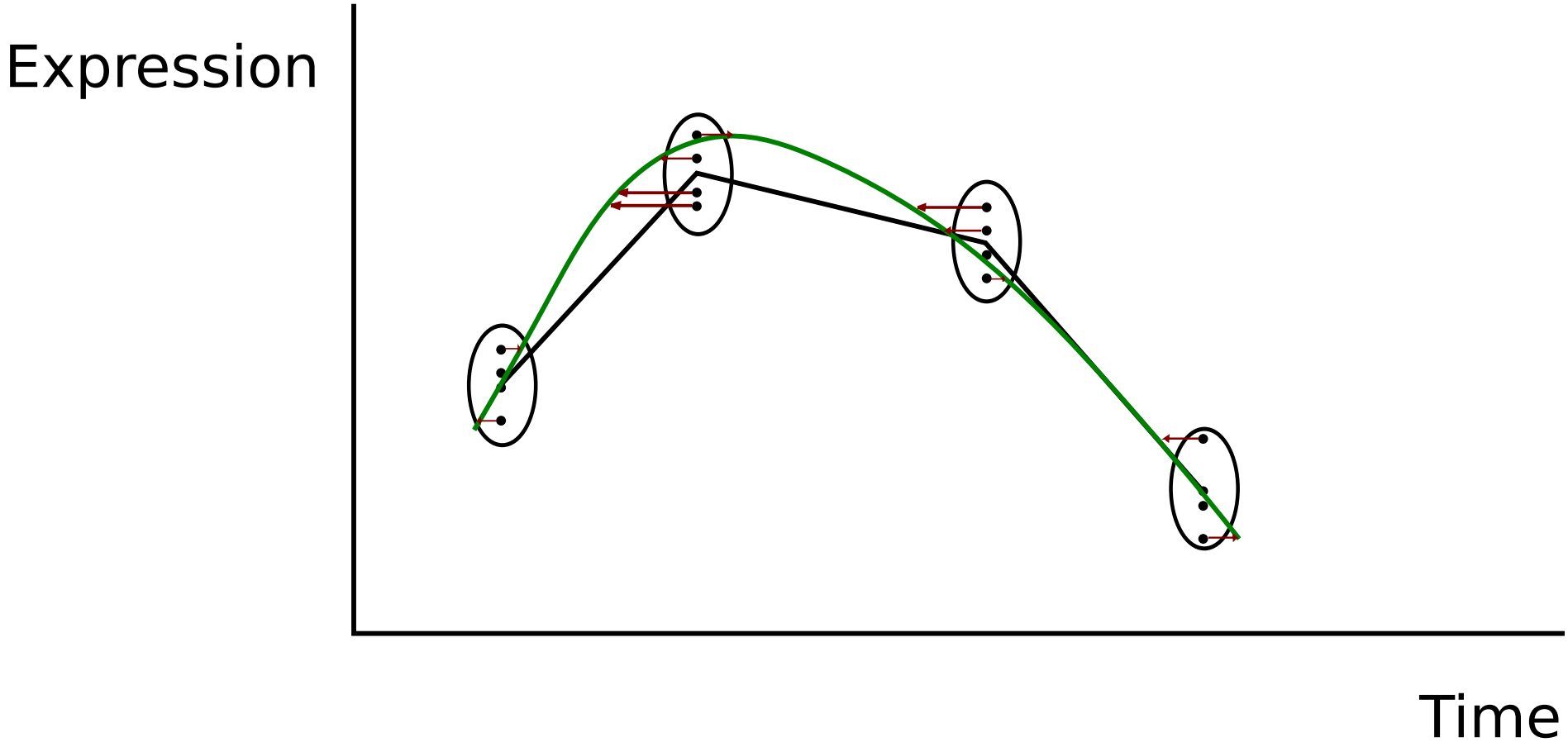
Time series – per gene/metabolite



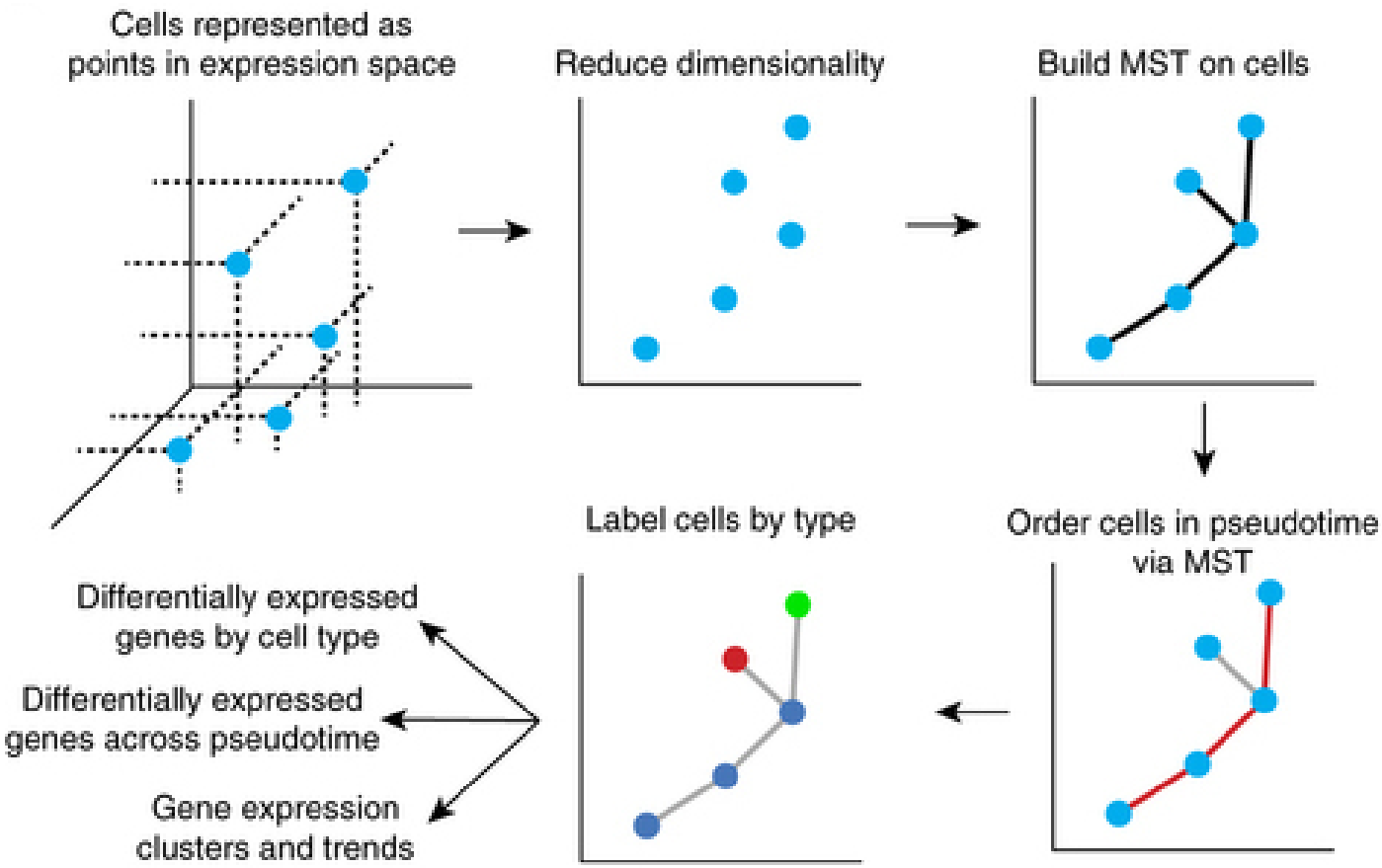
Time series problems

- For each measurement a mouse must be euthanised.
- So, each replicate at each time-point comes from a different mouse.
- Mice may develop at different rates or have varying metabolic rates.
- Therefore, at each time point replicates may be at different developmental stages.
- Solution? Pseudotemporal ordering.

Pseudotemporal ordering



Pseudotemporal ordering



Trapnell, C. et al. (2014). *The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells.* Nature Biotechnology, 32(4), 3816.

Pseudotemporal ordering

Pseudotemporal ordering also has the benefit of:

- giving a smoother profile and
- increasing the number of time points.

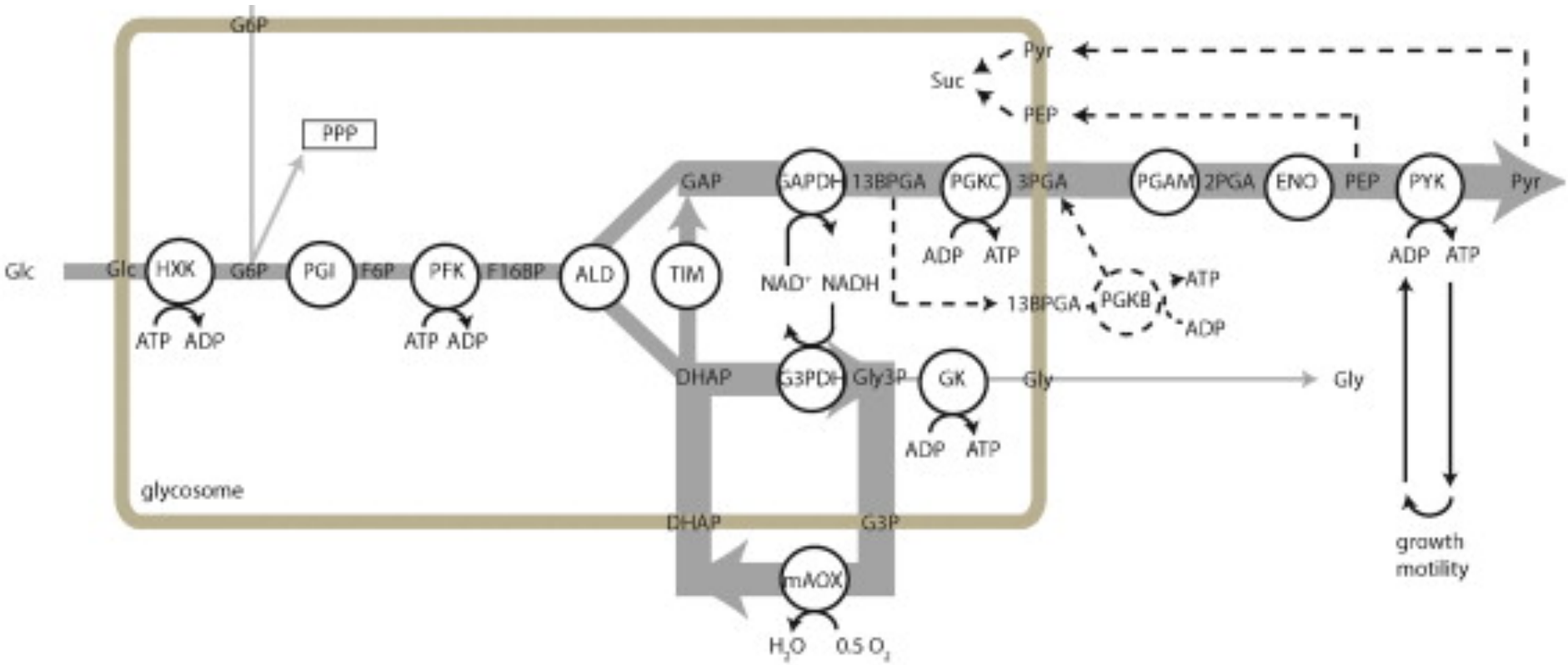
Both of which are desirable for dynamical modelling and parameter fitting.

First steps

- Take a candidate pathway
  - with known structure and
  - build a model—
  - in process algebra? (Of course!)
- Fit model parameters
  - to the relevant expression/metabolite profiles.

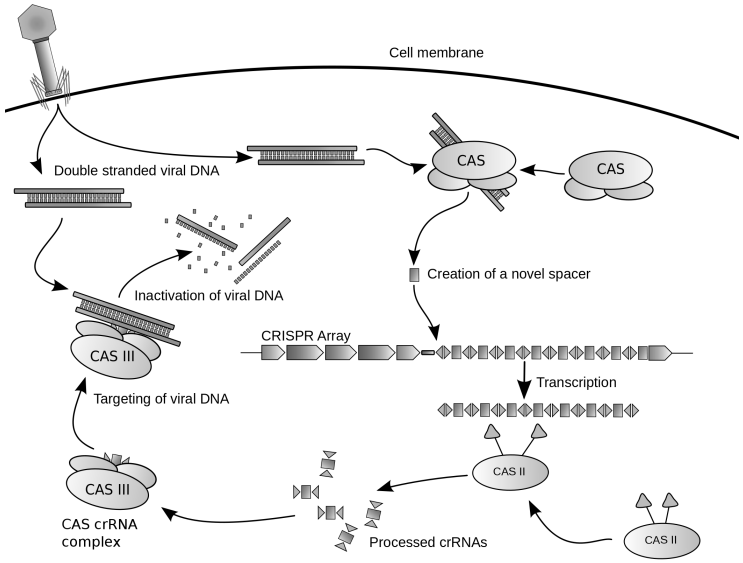
Glucose pathway

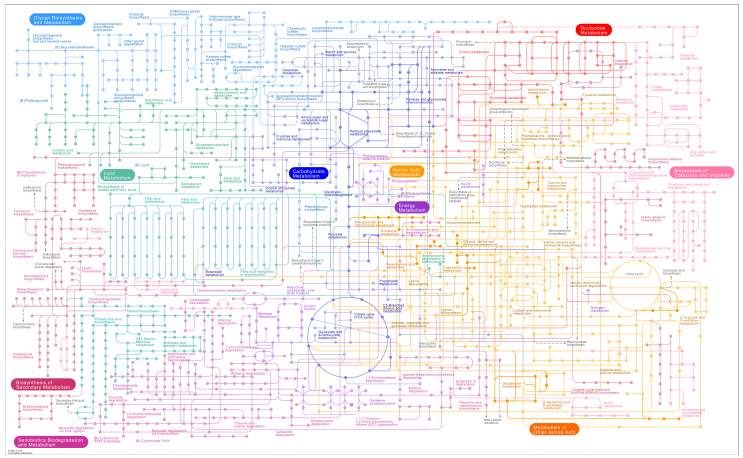
- A good starting point will be the glucose pathway.
- Trypanosome infection has a marked effect on the glucose pathway.
- Tryps cannot manufacture glucose, they take it from the host.



Next steps

- Predictive modelling: e.g. can we favourably alter glucose response by modifying genes? (Crispr?)
- Other metabolic pathways.
- We have data on large numbers of genes/metabolites:
  - can we infer new gene regulatory networks involved in the host-parasite interaction?





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THE ROYAL SOCIETY
EXCELLENCE IN SCIENCE

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