Variational kinetics: a variational formulation of reaction kinetics

Intelligent Systems for Molecular Biology
& European Conference on Computational Biology
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Recon4IMD

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Ollscoil na Gaillimhe
University of Galway

Outline

- Problem statement:
  - how to combine the strengths and overcome the weaknesses of constraint-based and kinetic modelling of biochemical networks?
- 2009-2011:
  - reformulations, exploration of convex optimisation, monotonicity, impasse.
- 2012-2022:
  - ~ “Shut up and calculate” thermodynamically feasible states
  - experimental validation
- 2023-2025
  - conic optimisation
  - numerical results

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  - ~ “Shut up and calculate” thermodynamically feasible states
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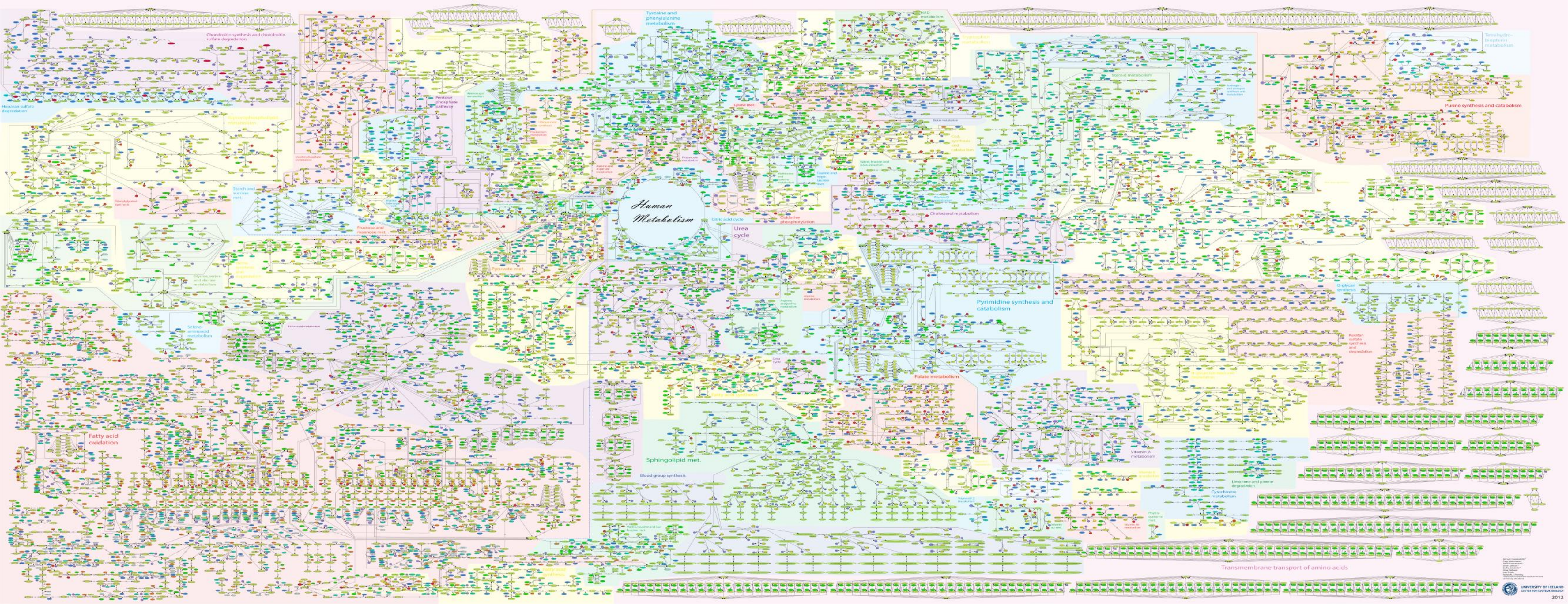
- 2023-2025
  - conic optimisation
  - numerical results
  - “A scare at bedtime”
  - relief – global convergence
- 2025+
  - Future work

Podge and Rodge “A scare at bedtime” (2011)

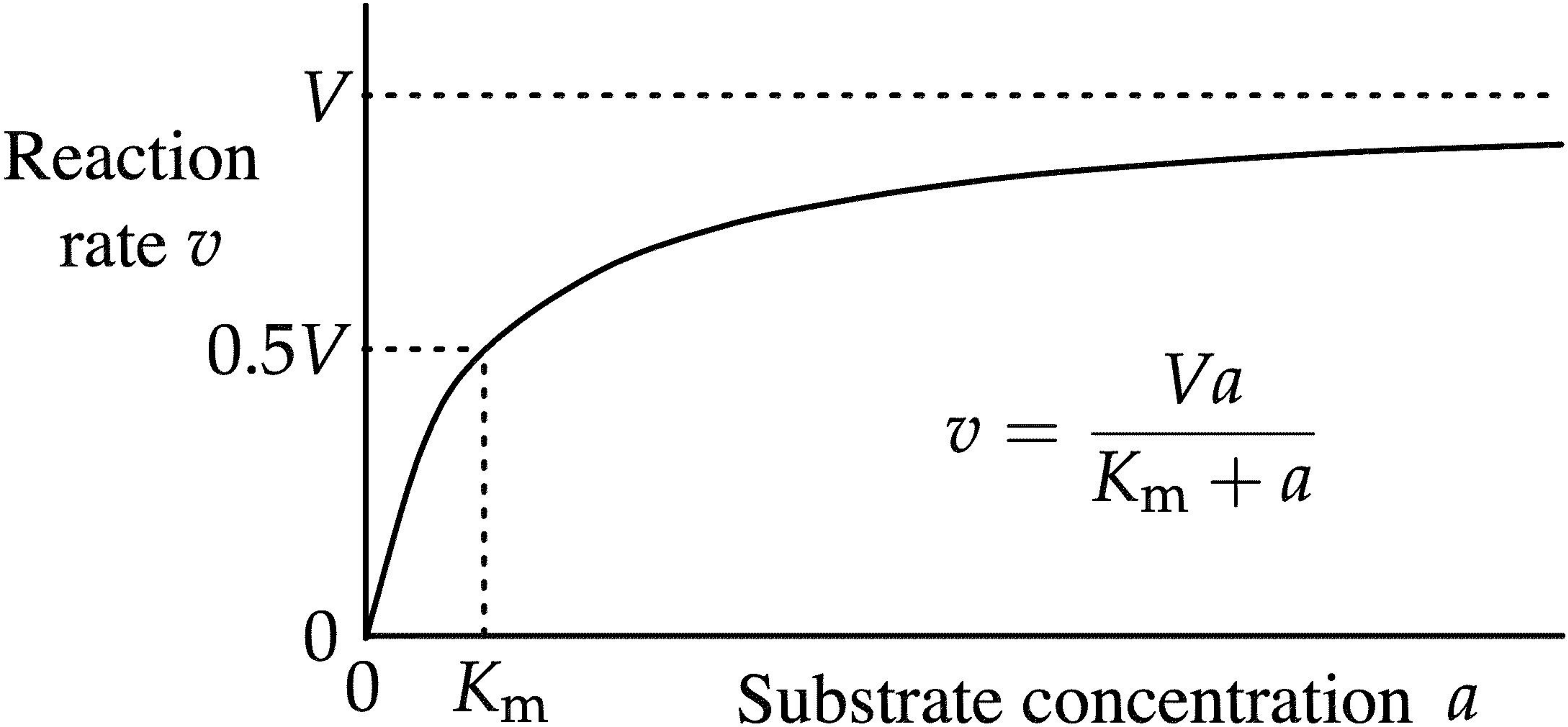
A paradox in genome-scale modelling

- existing genome-scale modelling methods only explicitly model reaction rate but not molecular species abundance
- experimental omics data measure molecular abundance and not reaction rate

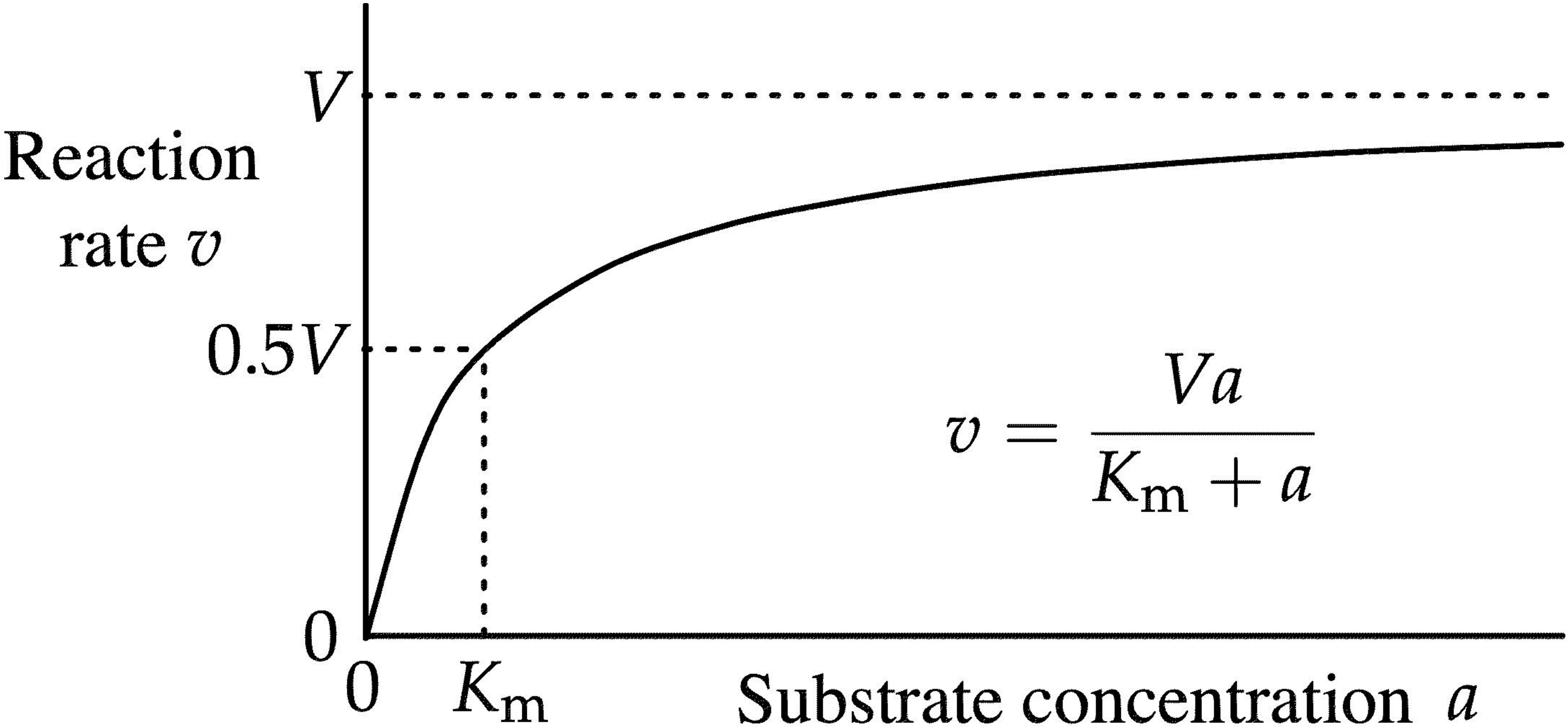


Noronha A., et. al. ReconMap: An interactive visualisation of human metabolism, Bioinformatics, 2016.

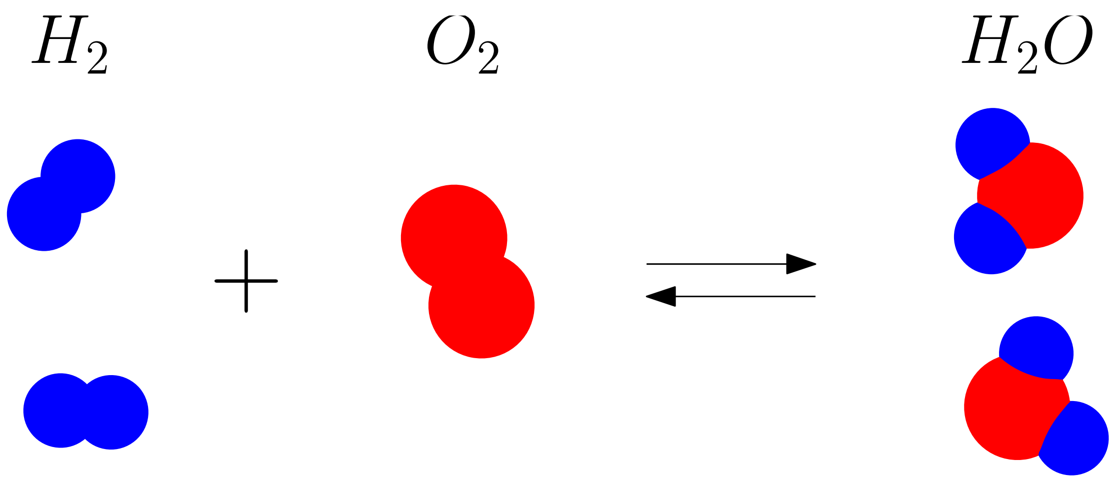
How to constrain genome-scale models with reaction kinetics?



How to extend reaction kinetics to genome-scale?

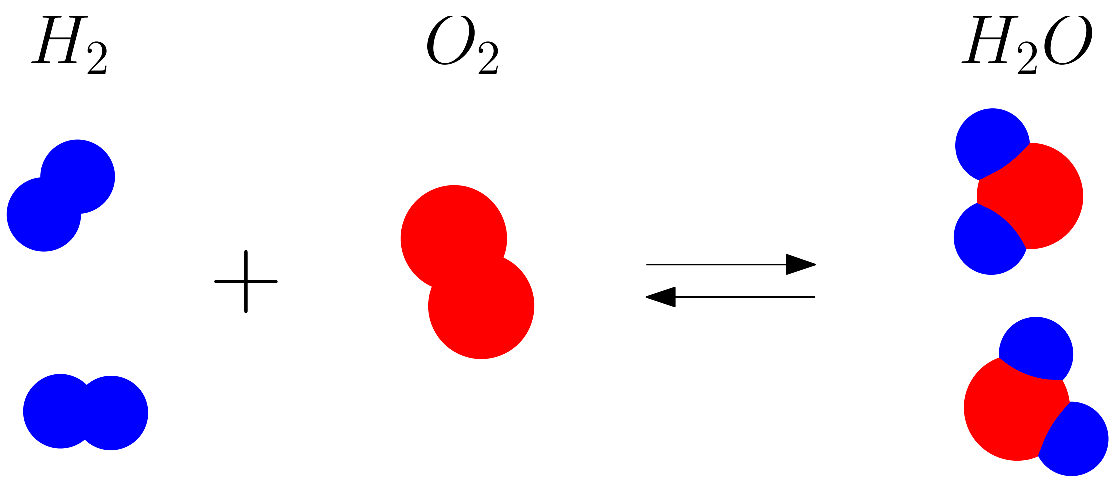


The utility of the exponential & logarithmic function in (bio)chemistry



$$
\begin{aligned}
\exp(\ln(x)) &= x \\
\exp(x+y) &= \exp(x) \times \exp(y) \\
\ln(xy) &= \ln(x) + \ln(y) \\
xy = \exp(\ln(xy)) &= \exp(\ln(x) + \ln(y)) = \exp(\ln(x)) \times \exp(\ln(y)) \\
x^2 y = \exp(2\ln(x) + \ln(y)) &= \exp(2\ln(x)) \times \exp(\ln(y)) \\
\prod x_i^{a_i} &= \exp(a^T \ln(x))
\end{aligned}
$$

Matrix-vector formulation of elementary kinetics



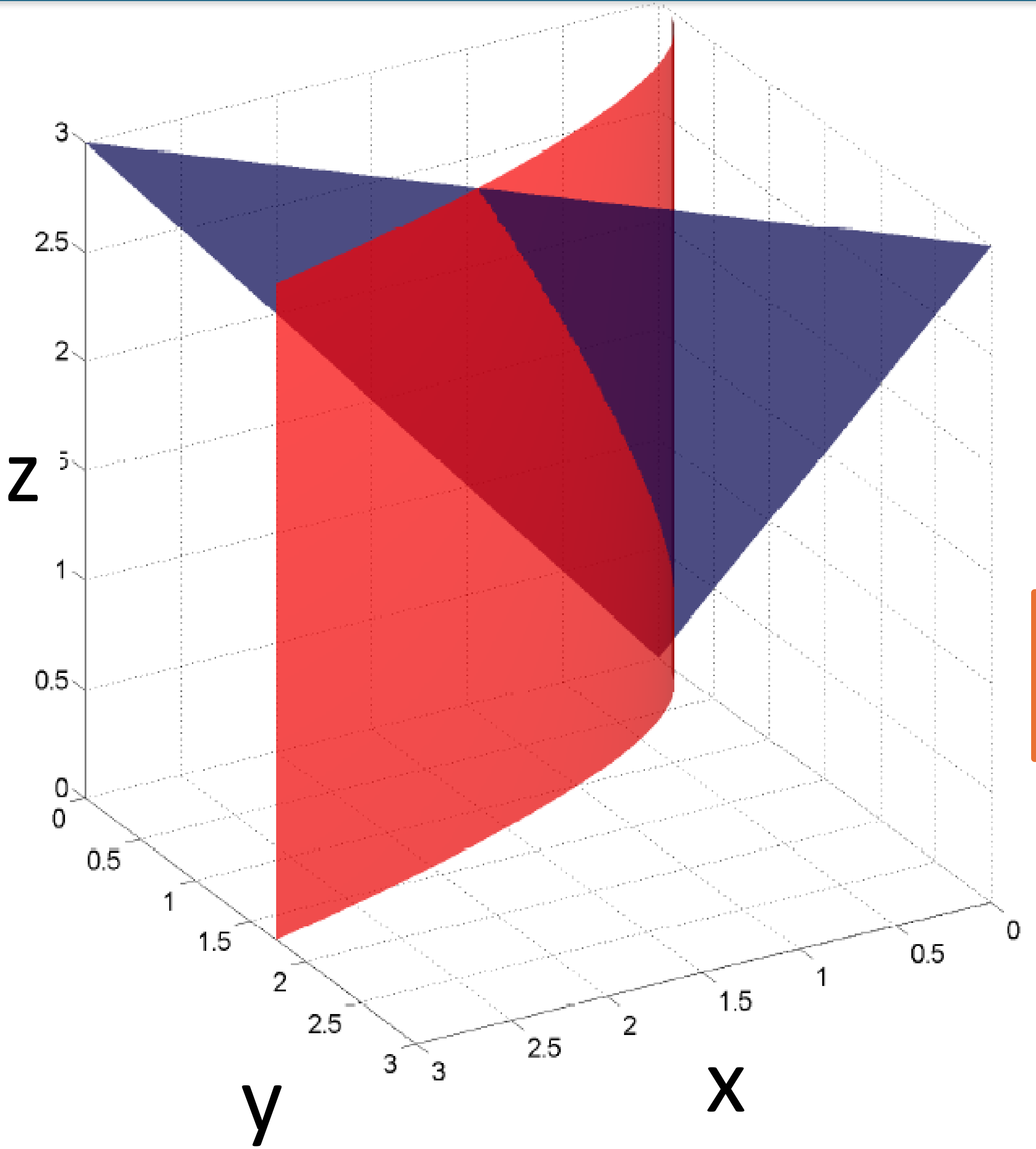
$$v_{net}(c, k_f, k_r) := v_f(c \mid k_f) - v_r(c \mid k_r)$$

$$N \in \mathbb{Z}^{m \times n} = -F + R$$

$$\begin{aligned} v_{fj}(c \mid k_{fj}) &:= k_{fj} \prod c^{F_{\mathrm{i,j}}} \\ v_{rj}(c \mid k_{rj}) &:= k_{rj} \prod c^{R_{\mathrm{i,j}}} \end{aligned}$$

$$\begin{aligned} v_f(c \mid k_f) &= \exp(\ln(k_f) + F^T \cdot \ln(c)) \\ v_r(c \mid k_r) &= \exp(\ln(k_r) + R^T \cdot \ln(c)), \end{aligned}$$

Steady state (linear) & kinetic equations (linear logarithmic)



$$\begin{bmatrix} 1 & 1 & -2 \end{bmatrix} \cdot \begin{bmatrix} x & y & z \end{bmatrix}^{\mathrm{T}} = 0.$$

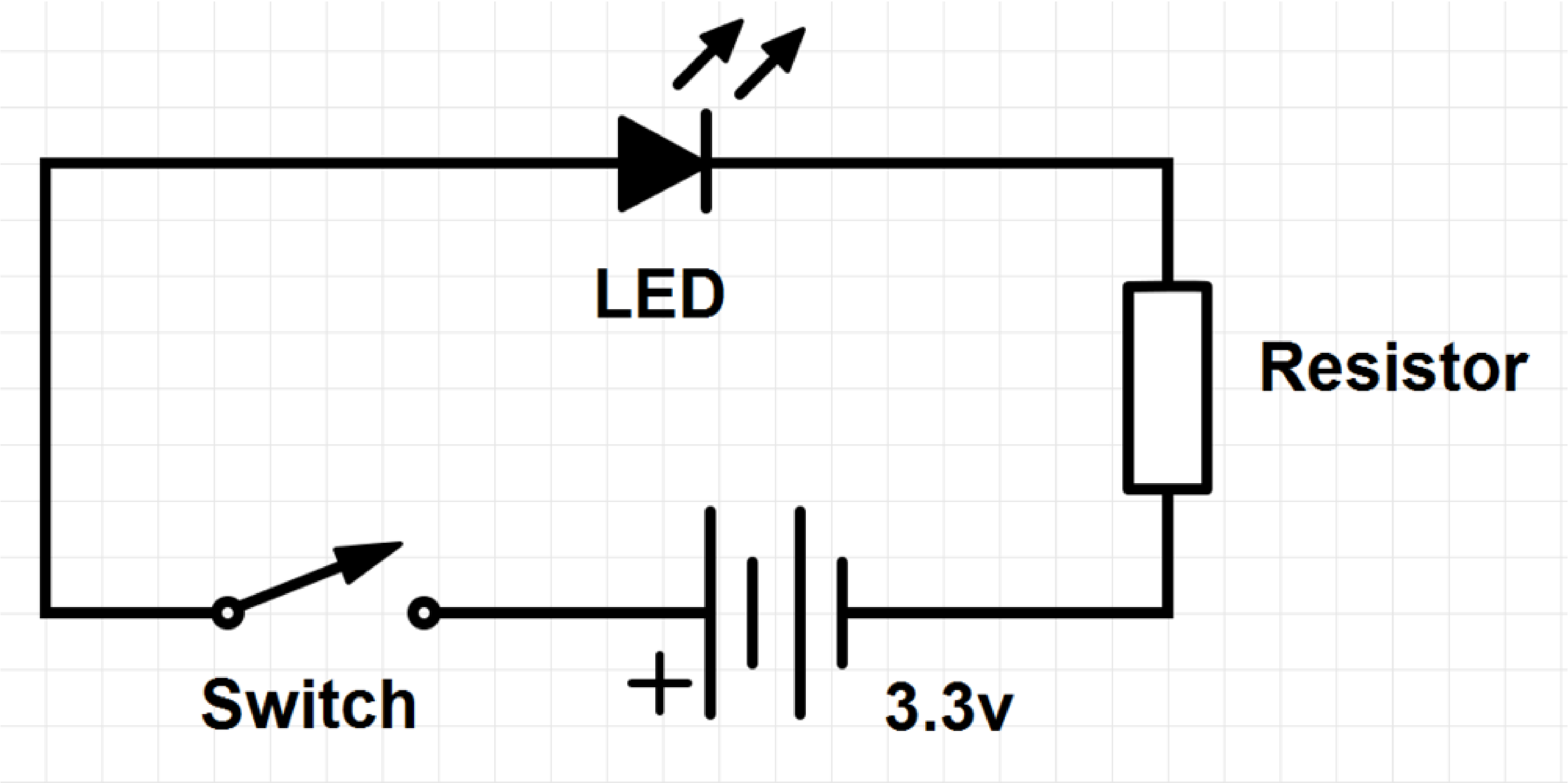
$$\begin{bmatrix} 1 & -2 & 0 \end{bmatrix} \cdot \begin{bmatrix} \ln(x) & \ln(y) & \ln(z) \end{bmatrix}^{\mathrm{T}} = 0.$$

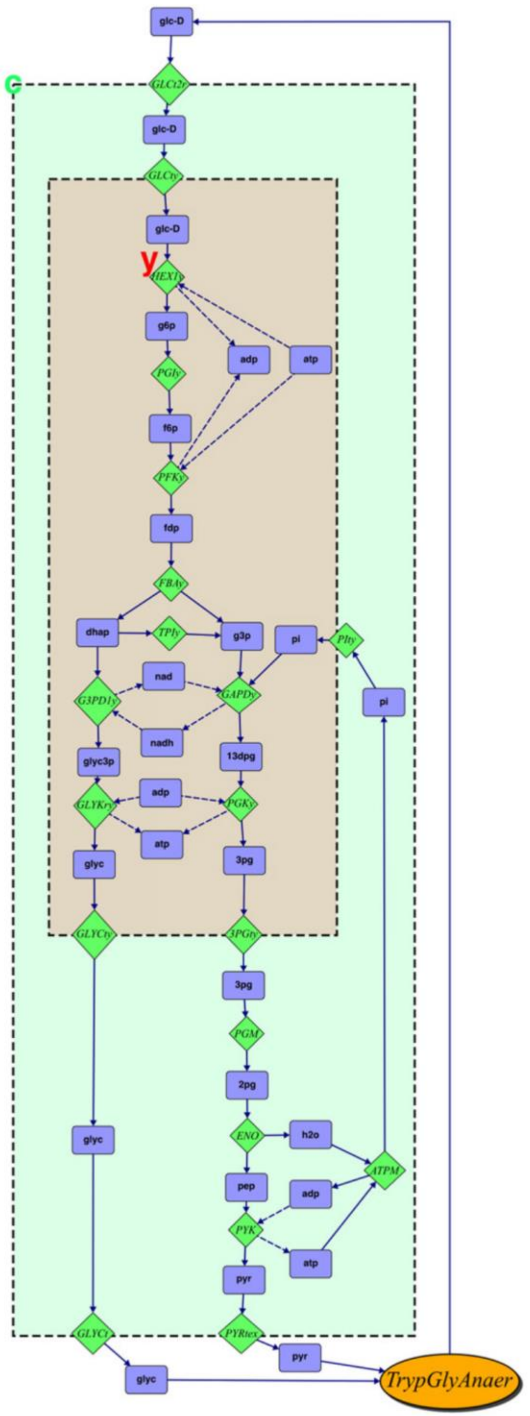
R.M.T. Fleming, I. Thiele, G. Provan, and H.P. Nasheuer. Integrated stoichiometric, thermodynamic and kinetic modeling of steady state metabolism. J. Theor. Bio., 264:683–92, 2010.

"The fundamental laws necessary for the mathematical treatment of a large part of physics and the whole of chemistry are thus completely known, and the difficulty lies only in the fact that application of these laws leads to equations that are too complex to be solved"

- Paul Dirac, Nobel Prize address, 1929.

When does a kinetic steady state exist?

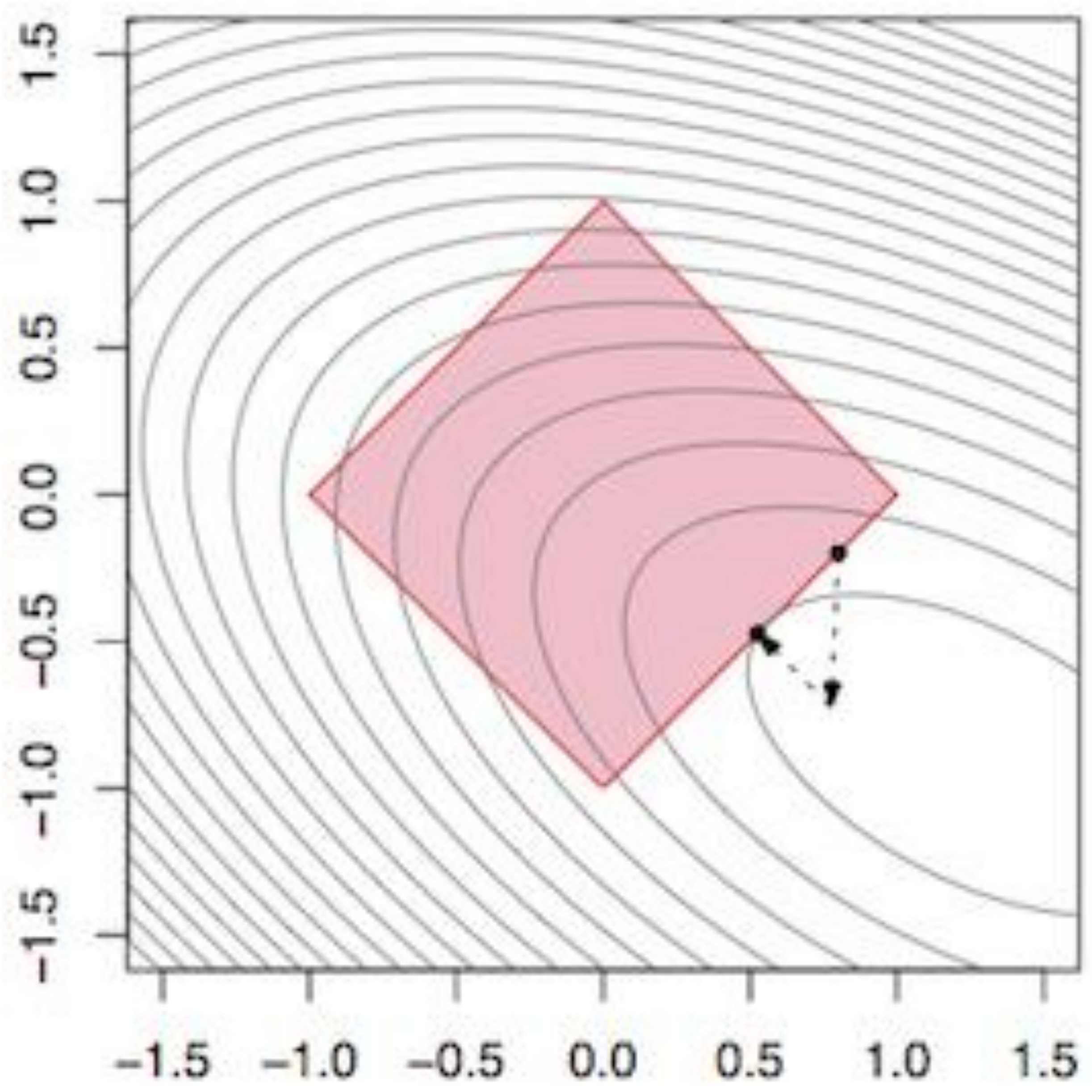


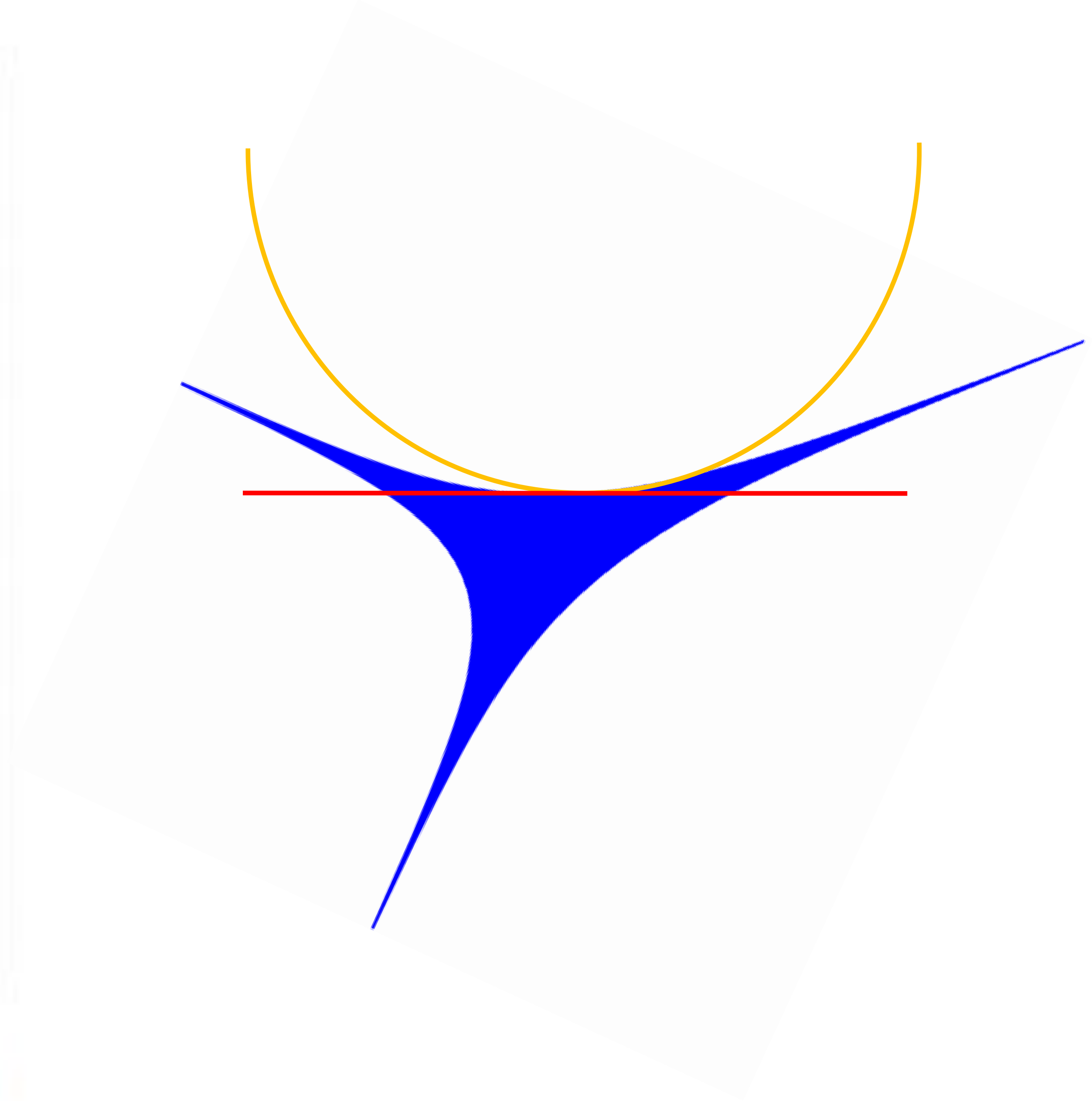


- ‘Mass Conserved Elementary Kinetics Is Sufficient for the Existence of a Non-Equilibrium Steady State Concentration’.
  - Assumes no bounds on reaction rates

Fleming, R.M.T., and I. Thiele. *Journal of Theoretical Biology* 314 (2012): 173–81

Convex optimisation – linear constraints, convex objective





Journal of Theoretical Biology 292 (2012) 71–77

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Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

A variational principle for computing nonequilibrium fluxes and potentials in genome-scale biochemical networks

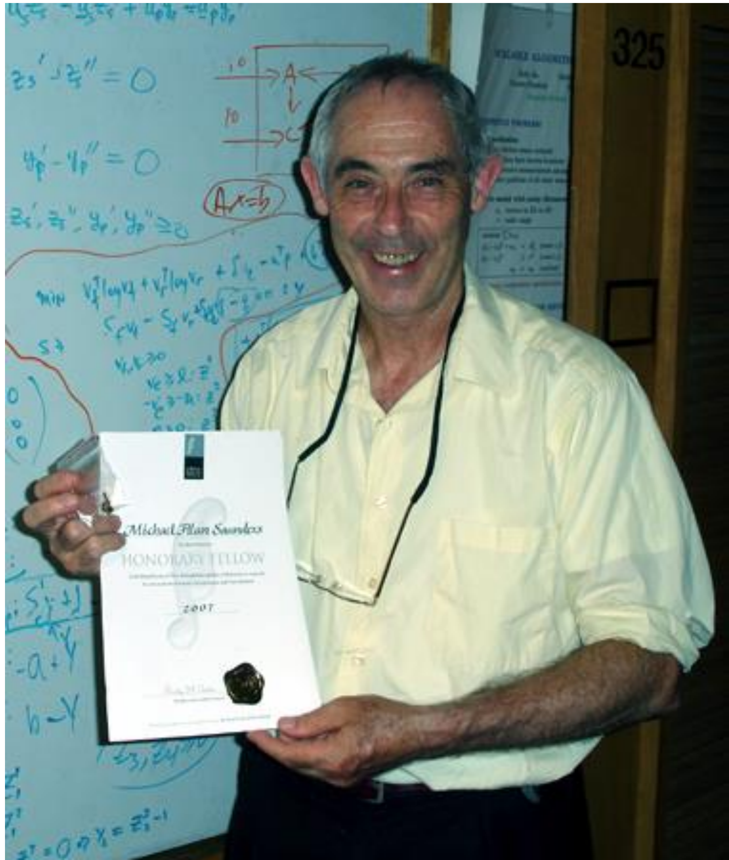
R.M.T. Fleming [a,*], C.M. Maes [b], M.A. Saunders [c], Y. Ye [c], B.Ø. Palsson [d]

Theorem 1. *Let $v_e^\star$ be any set of optimal exchange fluxes from problem (FBA). Define $b = -S_e v_e^\star$, and let c be any vector in $\mathbb{R}^n$. The convex equality-constrained problem*

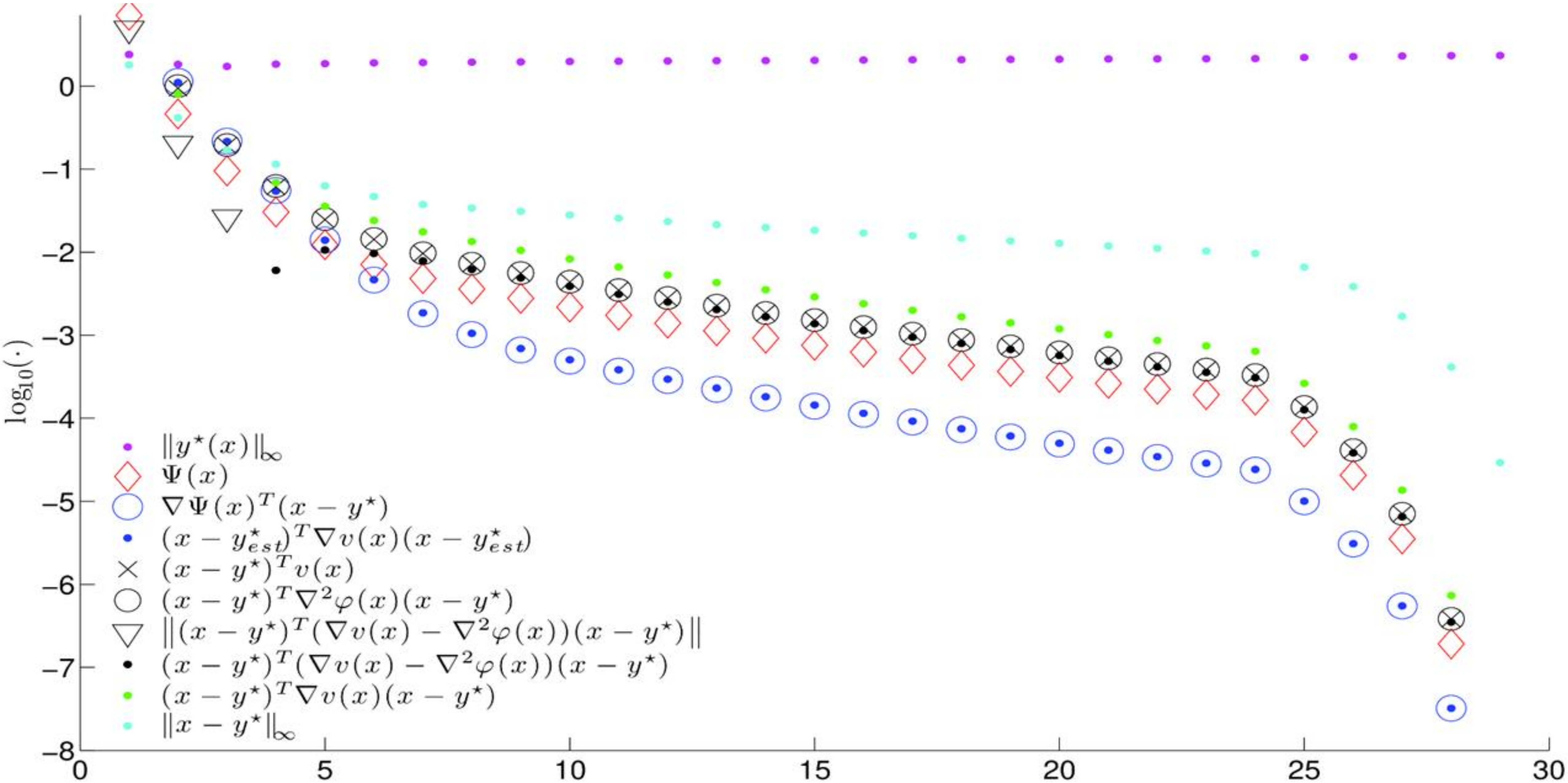
$$\begin{aligned} \underset{v_f, v_r > 0}{\text{minimize}} \quad & \phi \equiv v_f^T(\log(v_f)+c-e)+v_r^T(\log(v_r)+c-e) \\ \text{subject to} \quad & Sv_f - Sv_r = b : y \qquad \text{(EP)} \end{aligned}$$

is then feasible, and its solution $(v_f^\star, v_r^\star)$ is a set of thermodynamically feasible internal fluxes. The combined vector $(v_f^\star, v_r^\star, v_e^\star)$ is thermodynamically feasible and optimal for problem (FBA). The associated chemical potentials u may be obtained from the optimal Lagrange multiplier $y^\star \in \mathbb{R}^m$ for the equality constraints according to $u = -2\rho y^\star$.

Assumes no bounds on reaction rates

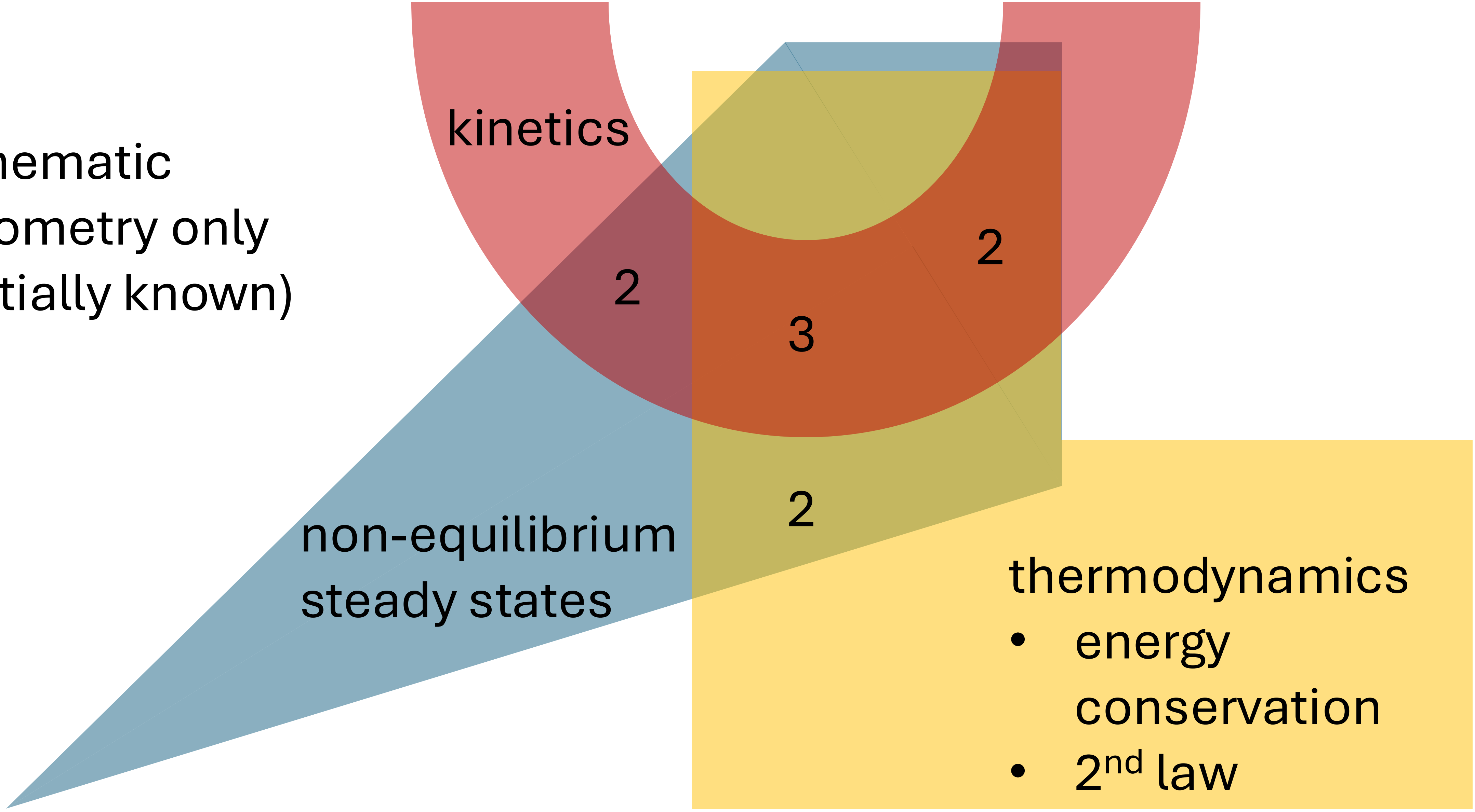


A sequence of convex optimisation problems

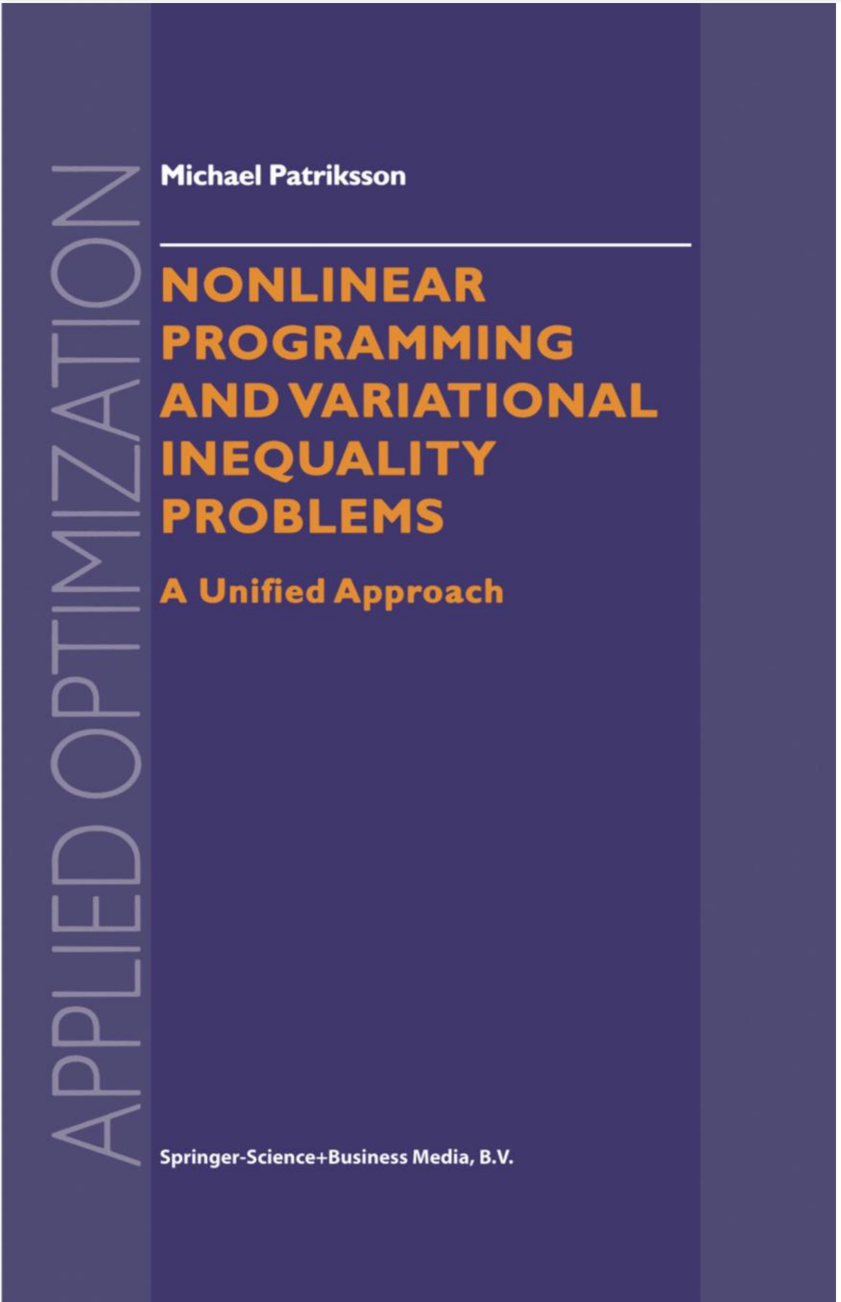


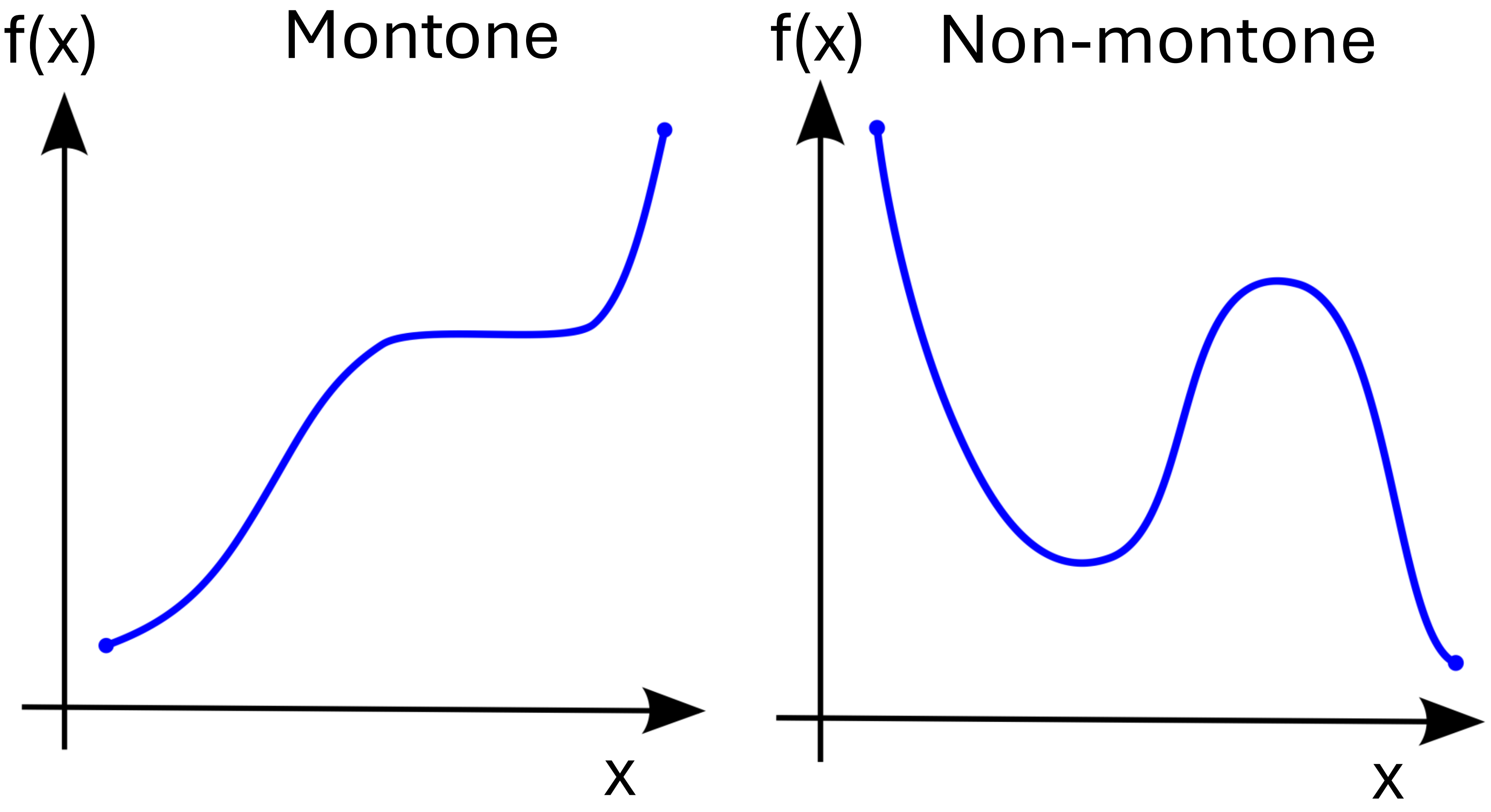
3 sequences of convex optimisation problems

Schematic
(geometry only
partially known)



Convergence of a convex optimisation sequence

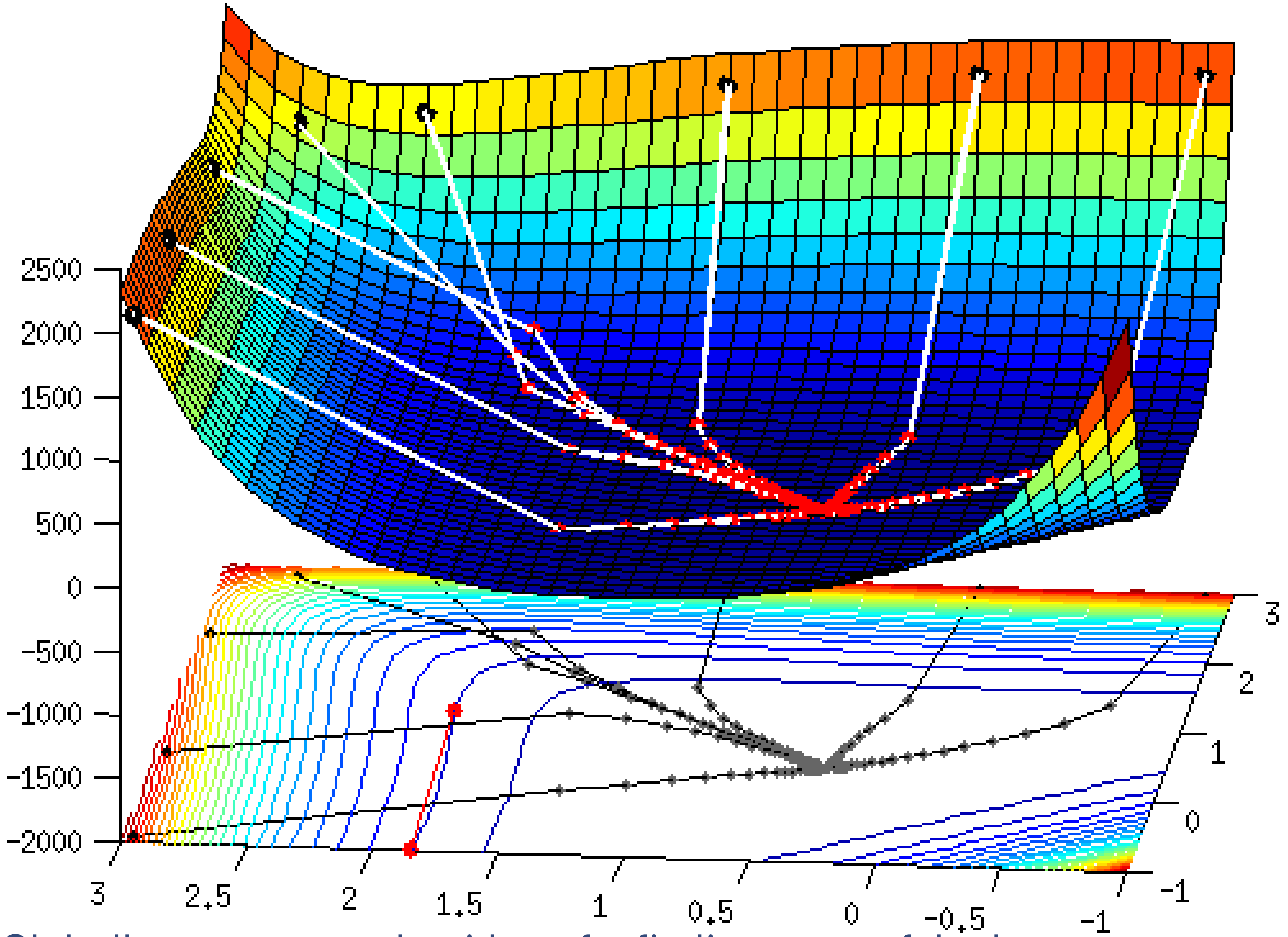




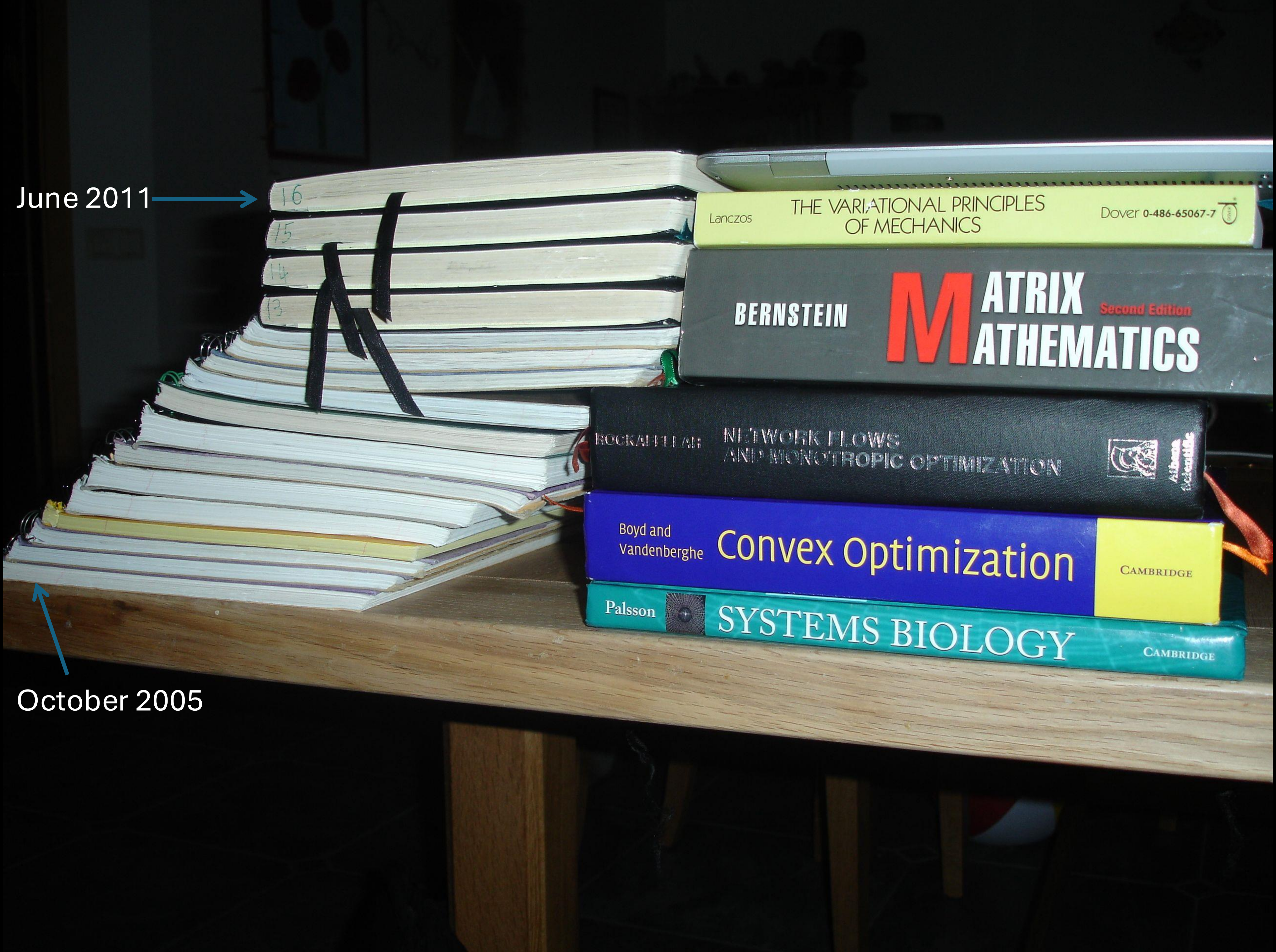
Global convergence: assuming duplomonotonicity

Monotone $\overset{\Rightarrow}{\not\Leftarrow}$ Duplomonotone $\quad f(x)^T \cdot \nabla f(x) \cdot f(x) \geq 0$

$f(x)^T \cdot f(x)$

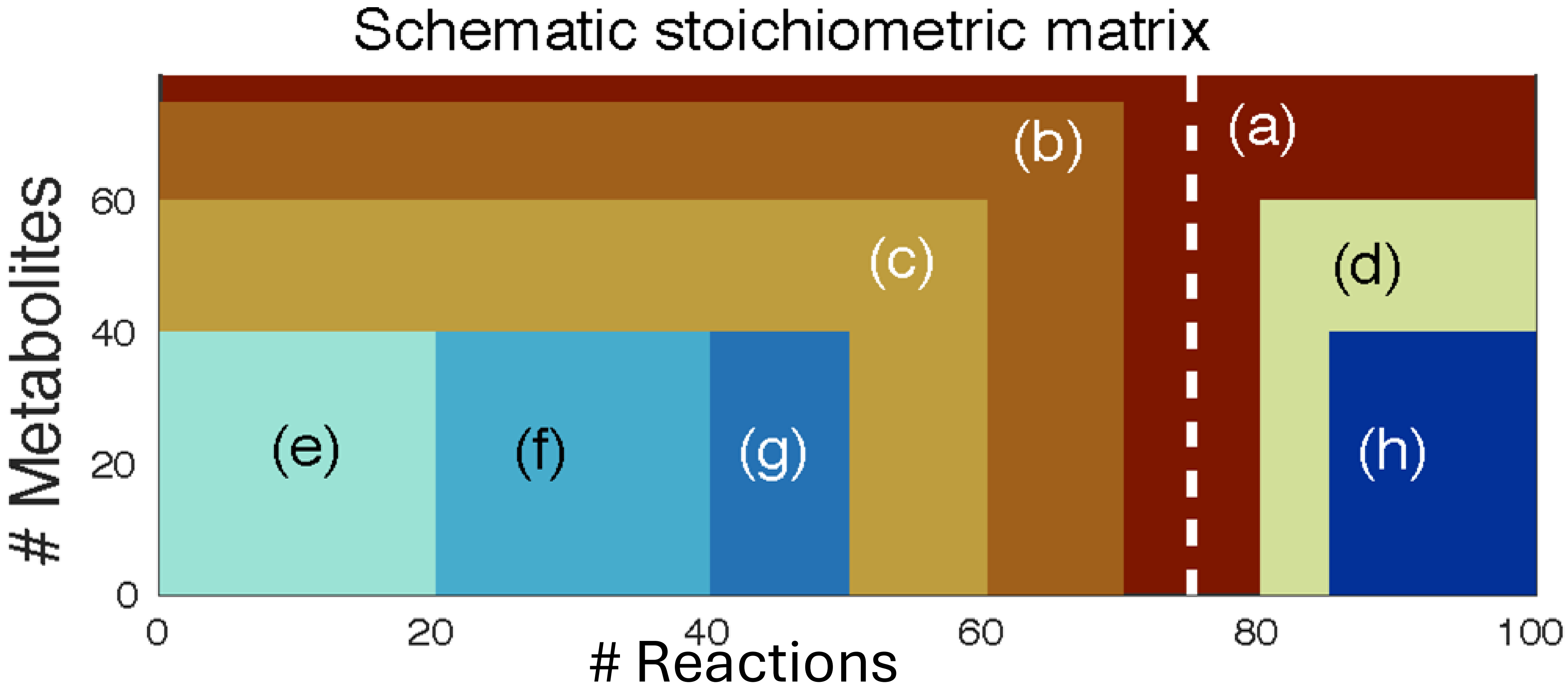


F.J. Aragón Artacho & R.M.T. Fleming, Globally convergent algorithms for finding zeros of duplomonotone mappings, Optimization Letters, (2015), 3(3), 569-584.


June 2011
October 2005
16
15
14
13
Lanczos
THE VARIATIONAL PRINCIPLES OF MECHANICS
Dover 0-486-65067-7
BERNSTEIN
MATRIX MATHEMATICS
Second Edition
ROCKAFELLAR
NETWORK FLOWS AND MONOTROPIC OPTIMIZATION
Athena Scientific
Boyd and Vandenberghe
Convex Optimization
CAMBRIDGE
Palsson
SYSTEMS BIOLOGY
CAMBRIDGE

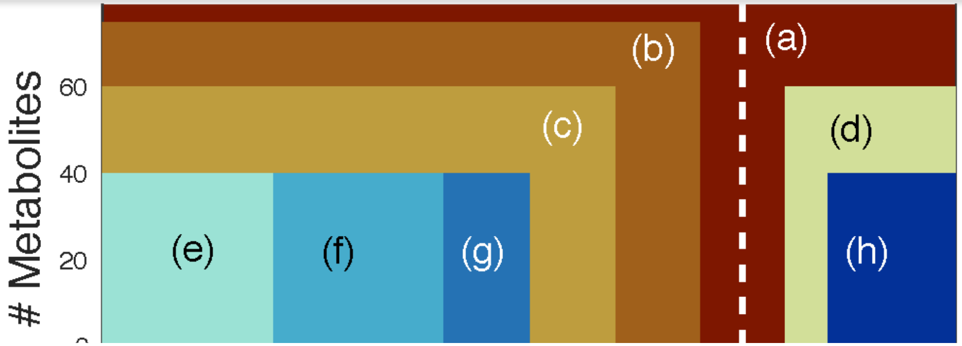
Thermodynamic feasibility is necessary for mass action kinetics

(a) reconstruction
(b) stoichiometrically consistent subset
(c & d) + internal and external flux consistent
(e, f, g, h) + both, forward, reverse, external thermodynamically flux consistent



Fleming, R.M.T. et al *Bioinformatics* 39, no. 9 (2023) https://doi.org/10.1093/bioinformatics/btad450.

Metabolic reconstruction versus metabolic models

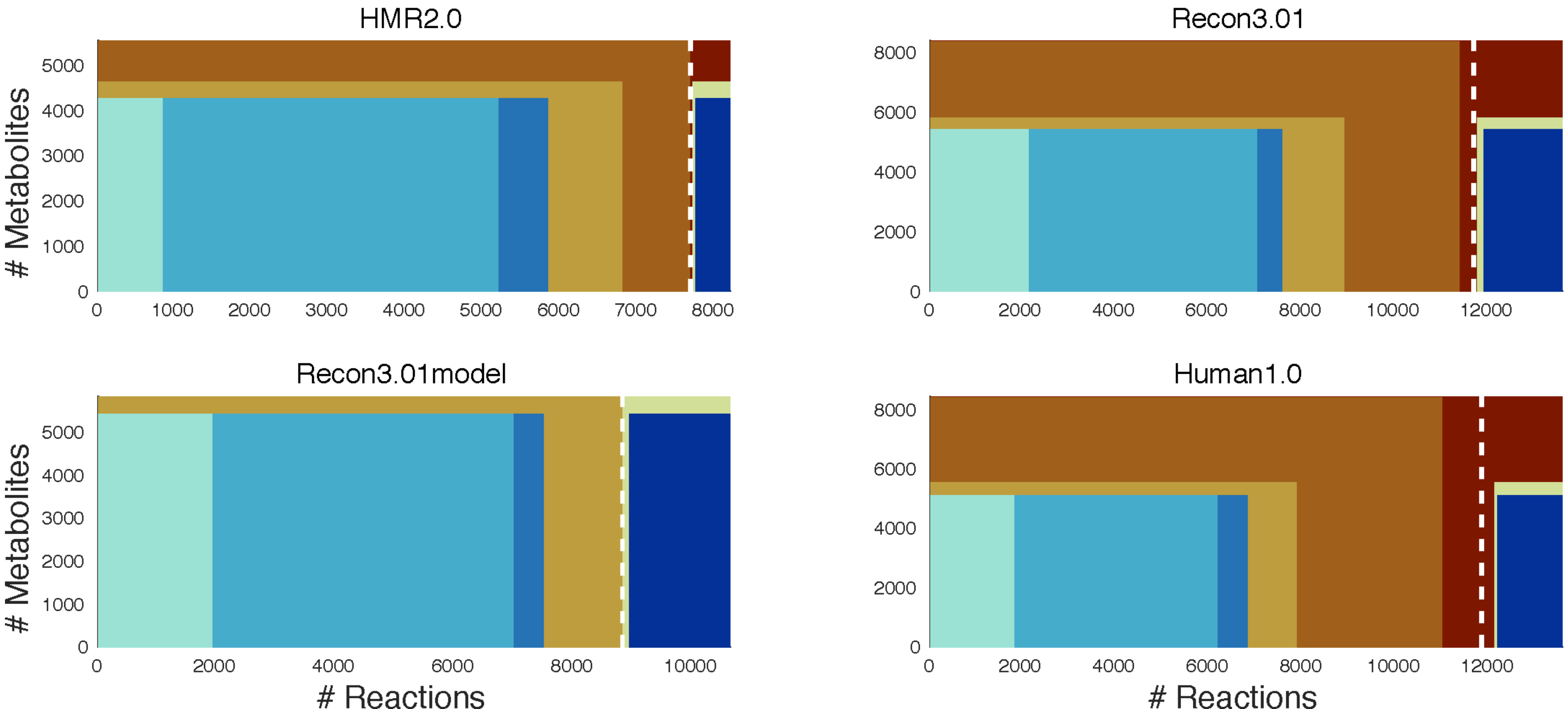


(a) reconstruction

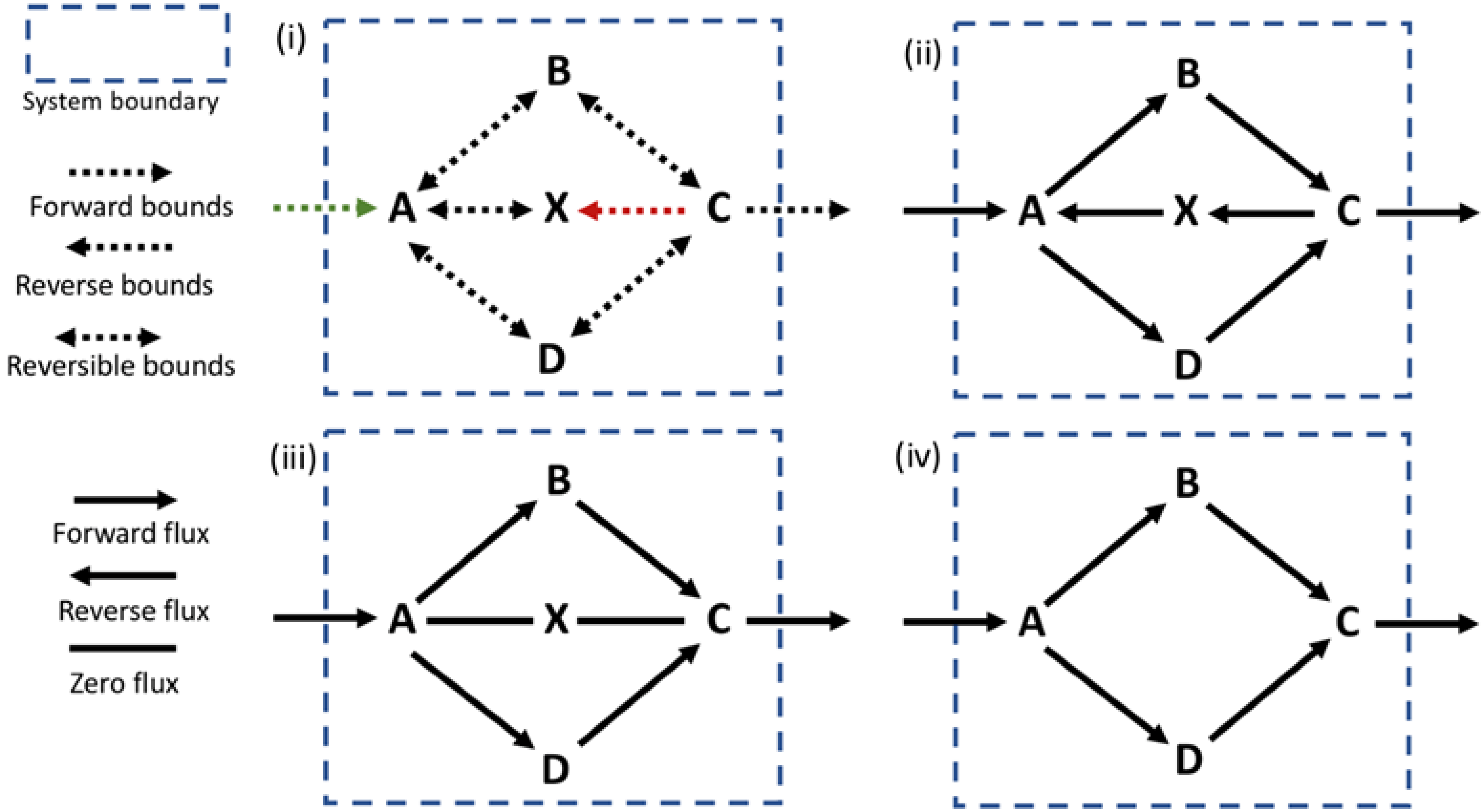
(b) stoichiometrically consistent subset

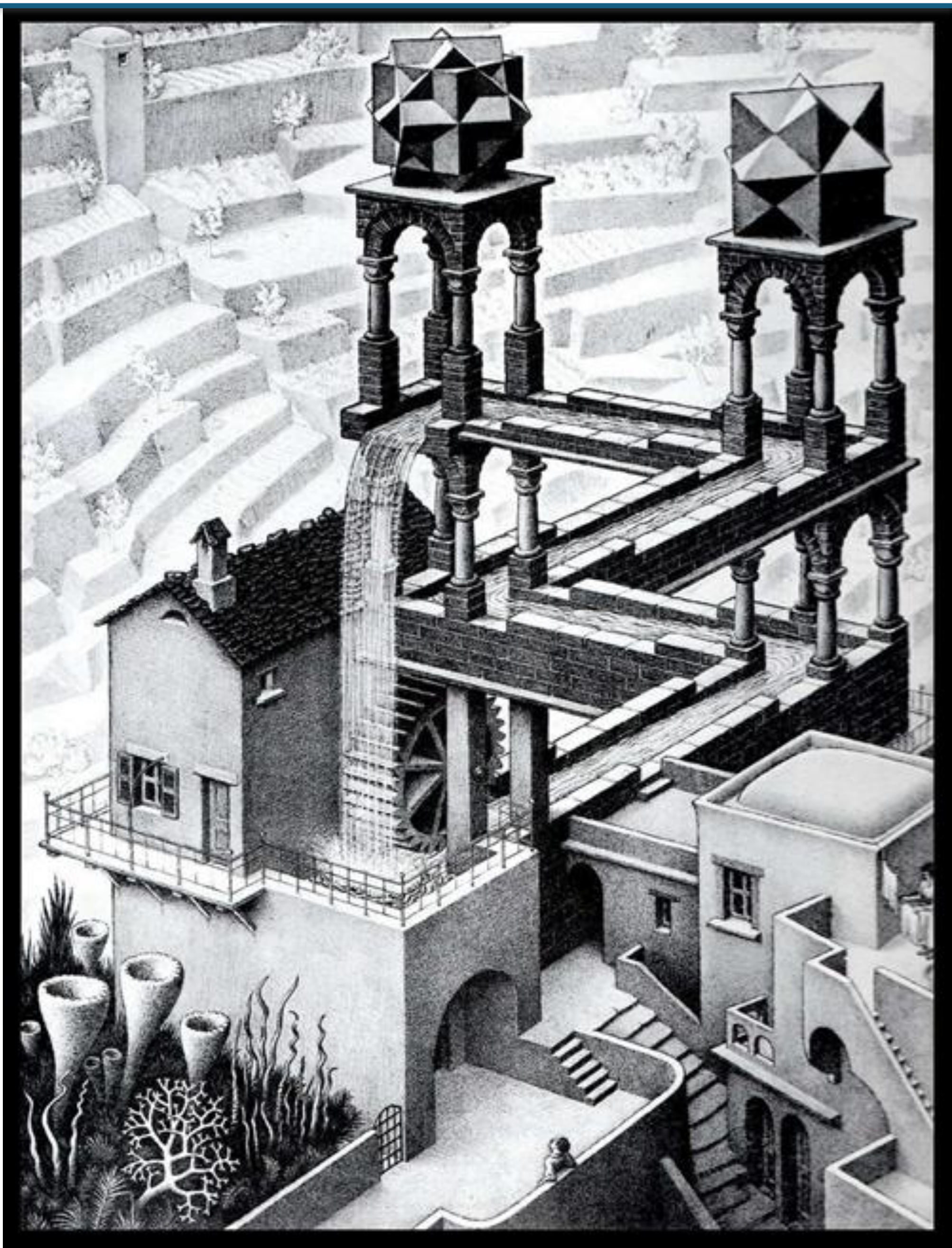
(c, d) + flux consistent

(e, f, g, h) + thermodynamically flux consistent



Thermodynamic flux consistency ensures thermodynamic feasibility



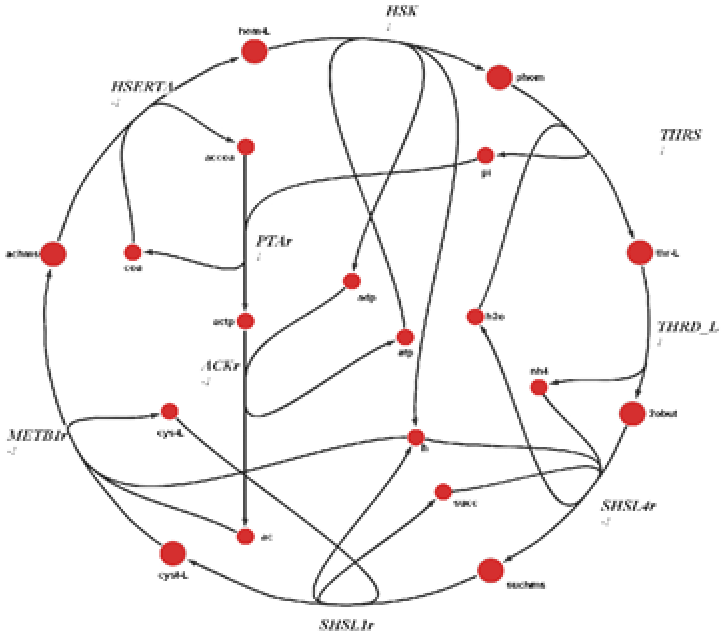


Fleming, R.M.T. et al 'Cardinality Optimization in Constraint-Based Modelling: Application to Human Metabolism'. *Bioinformatics* 39, no. 9 (2023) https://doi.org/10.1093/bioinformatics/btad450.

thermoKernel: a novel thermodynamically consistent model extraction algorithm

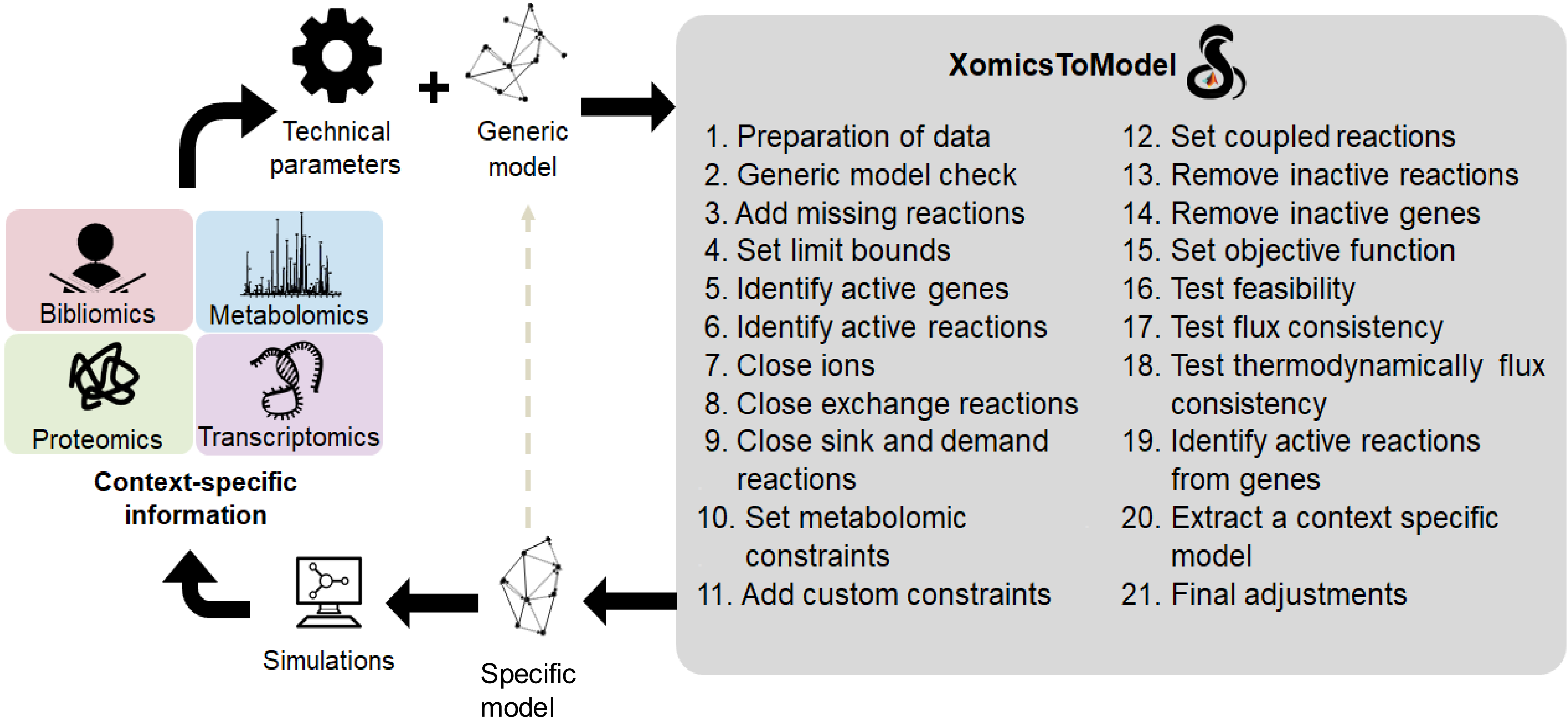
- **New options for input data**
  - presence/absence of metabolites (not just reactions or genes) to be specified
  - weights on metabolite/reaction/genes
    - e.g. transcript abundance

- **Improved context-specific model output**
  - all reactions are thermodynamically flux consistent
    - admits a flux satisfying energy conservation
    - admits a flux satisfying 2nd law of thermodynamics
    - internal reaction rates can be predicted
    - admits reconstruction directionality constraints
  - minimal sized model
  - scalable: algorithm based on a sequence of linear optimization problems



Preciat, G., et al. XomicsToModel: Multiomics data integration and generation of thermodynamically consistent metabolic models.
Nature Protocols (to appear), 2025.

XomicsToModel: constraint-based models from multi-omic data



Nature Protocol (to appear) + COBRA Toolbox extension + tutorials and examples:

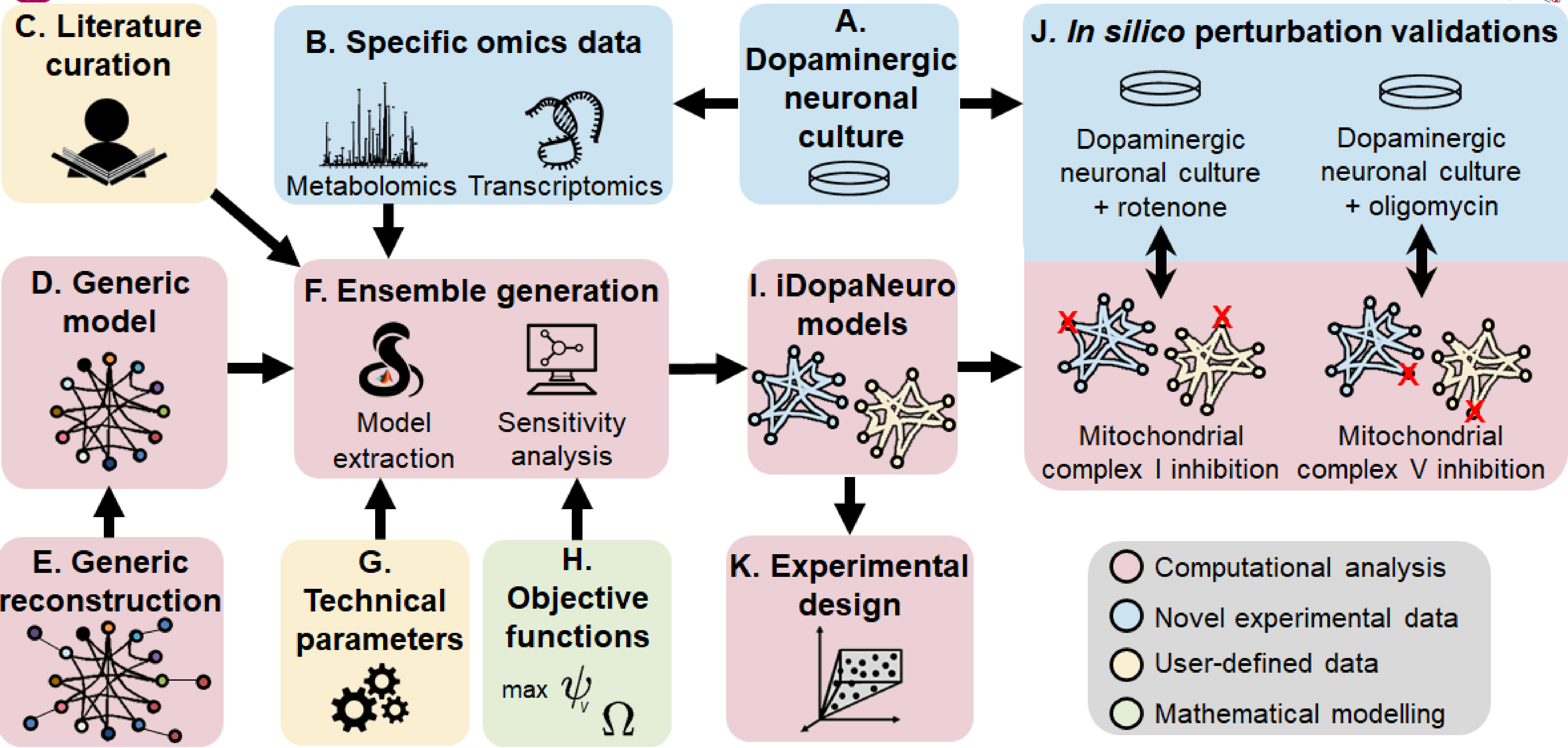
https://www.biorxiv.org/content/10.1101/2021.11.08.467803v2

https://github.com/opencobra/COBRA.tutorials/tree/master/dataIntegration/XomicsToModel

https://github.com/opencobra/cobratoolbox/tree/master/src/dataIntegration/XomicsToModel

https://github.com/opencobra/COBRA.papers/tree/master/2023_iDopaNeuro

Generic model + specific data + XomicsToModel → Specific model



Preciat G. et. al. Mechanistic model-driven exometabolomic characterisation of human dopaminergic neuronal metabolism, Comm. Biol. (to appear) https://doi.org/10.1101/2021.06.30.450562

Comparison of measured and predicted exchange fluxes for complex I inhibition.

- QEFBA = Quadratic penalisation of exchange flux deviation from measured exchanges with entropic flux balance analysis ()
- LOOCV = above approach except with omission of one experimentally measured exchange flux for each metabolite in the leave-one-out cross validation

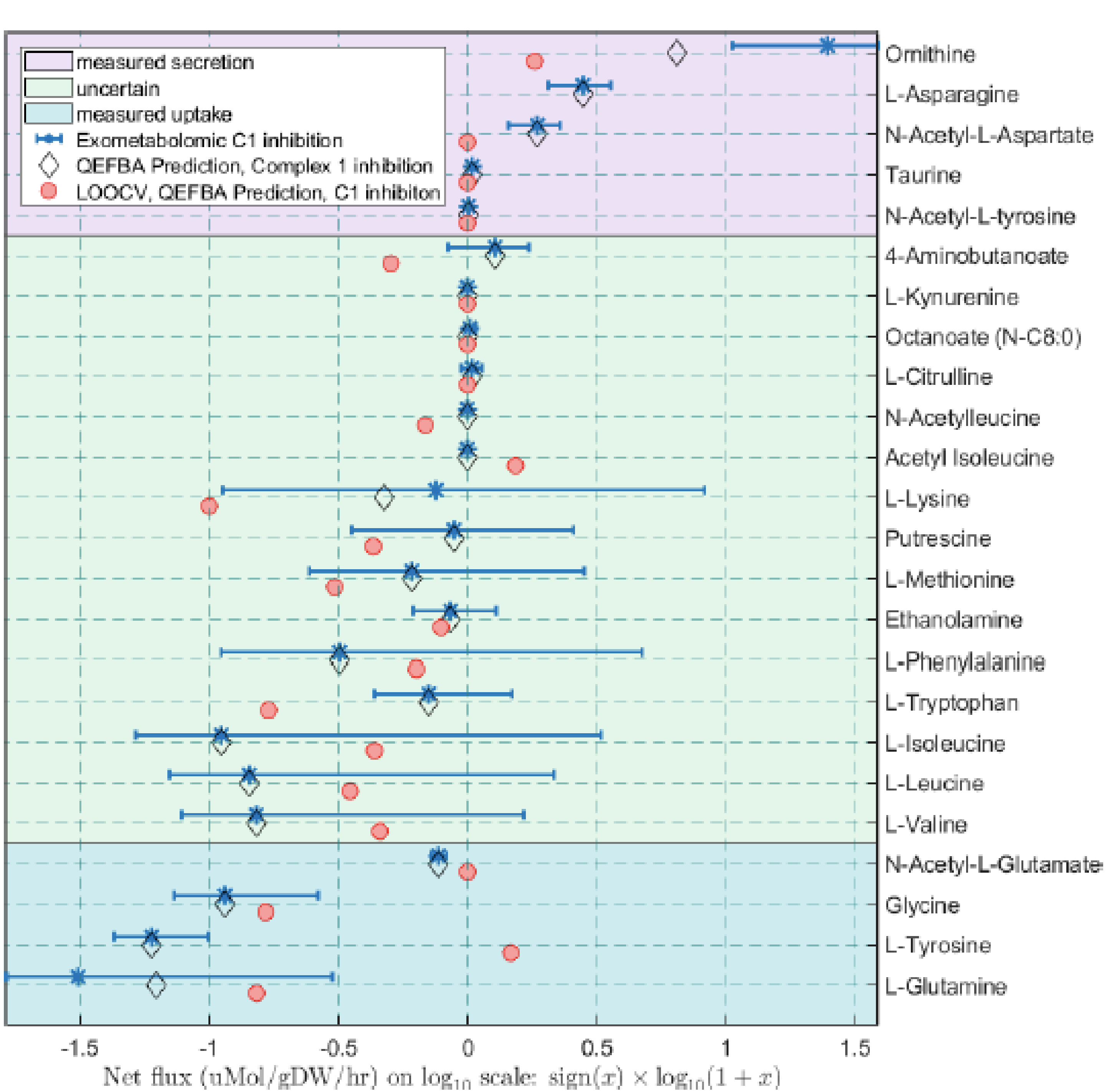
Qualitative accuracy:

- correct/total = 0.78, n = 9

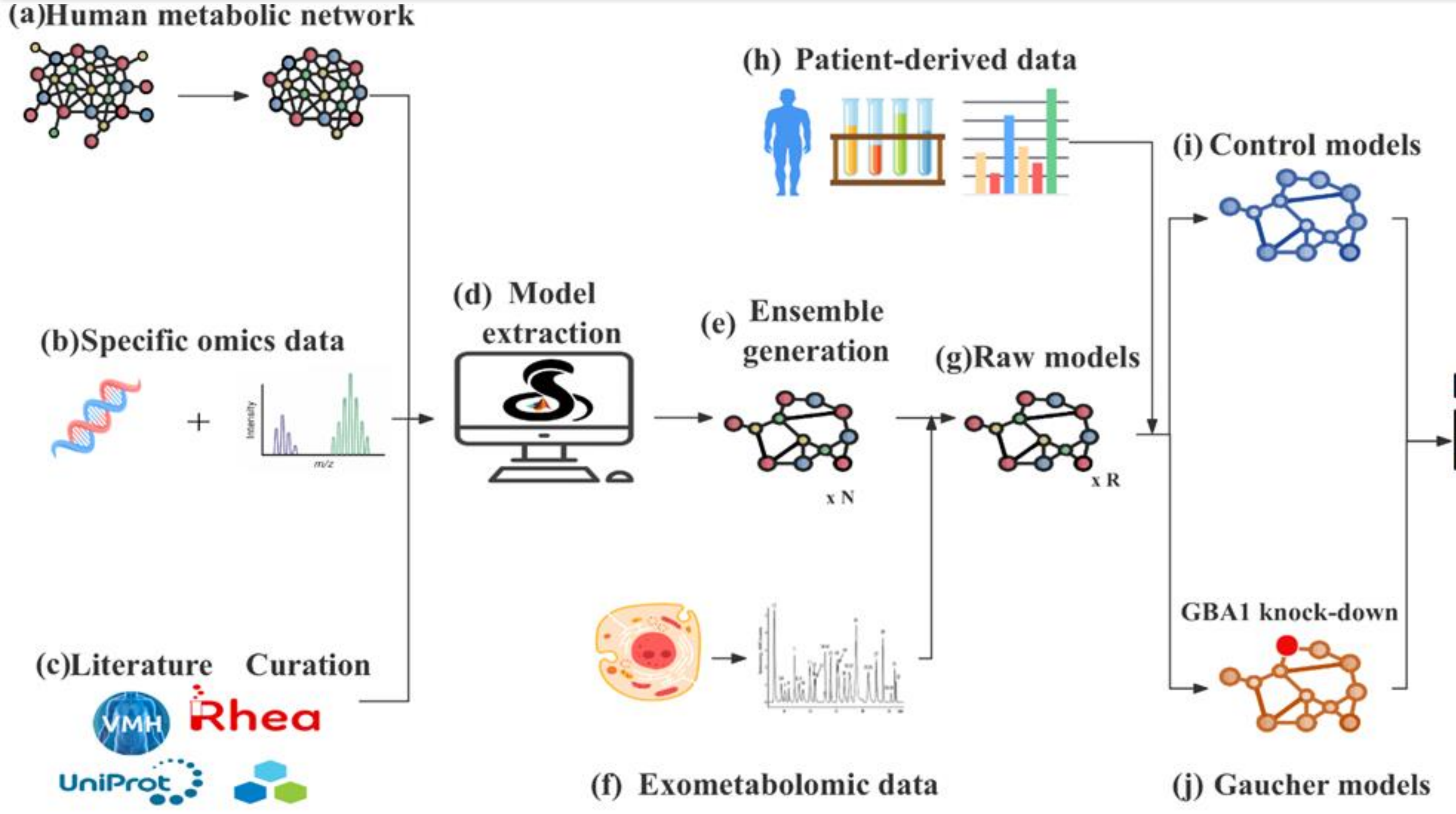
Semi-quantitatively accuracy:

- Spearman ρ = 0.48, $pval$ = 0.018

Preciat G. et. al. Mechanistic model-driven exometabolomic characterisation of human dopaminergic neuronal metabolism, Comm. Biol. (to appear) https://doi.org/10.1101/2021.06.30.450562



Constraint-based modelling of macrophages with Gaucher disease

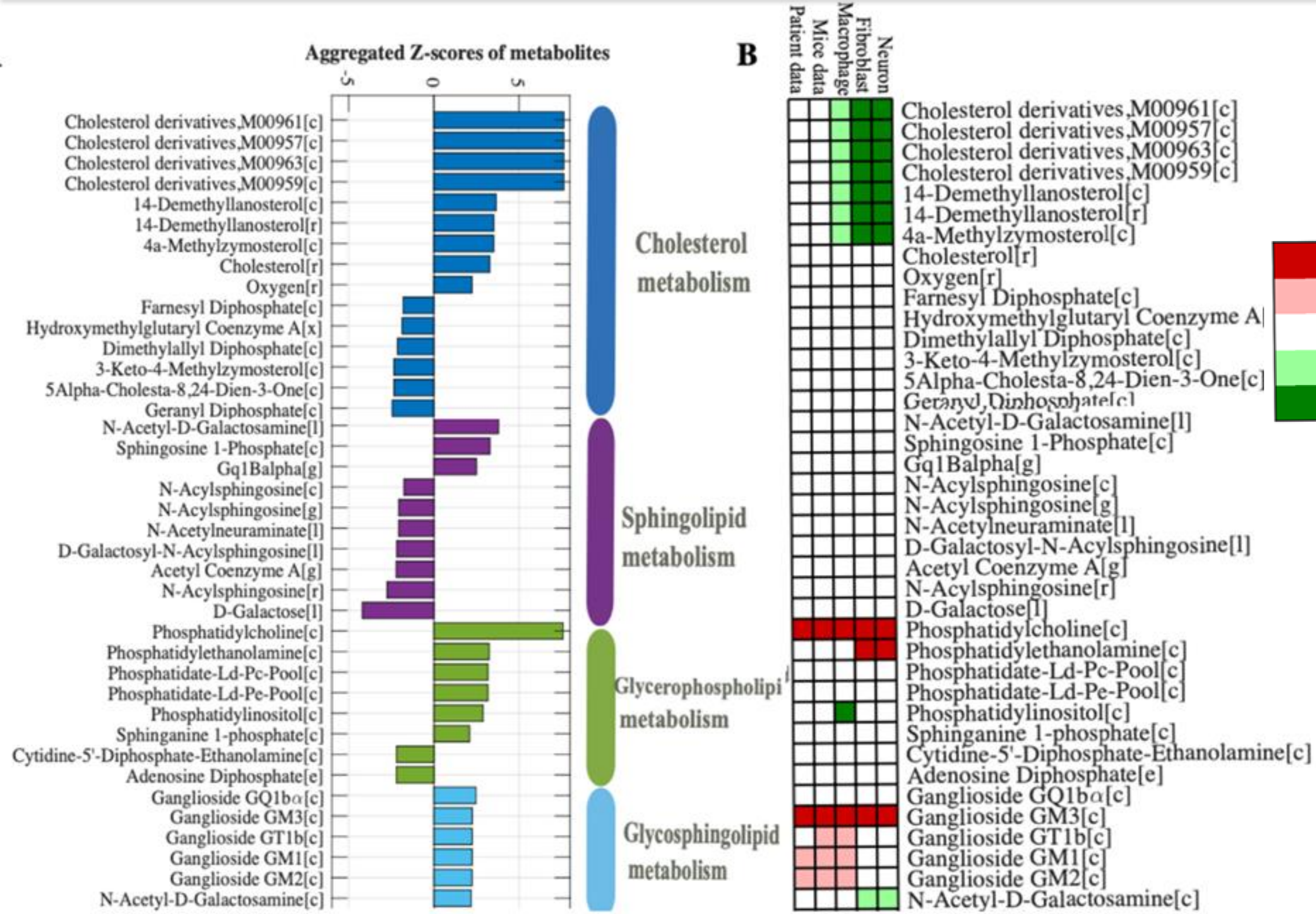


Y. Liu, Xi Luo, S. Ranjbar, M. van der Liende, J.M.F.G. Aerts, A. Dardis, R.M.T. Fleming, Constraint-based Modelling of Metabolic Dysregulation in Gaucher Disease: Mitochondrial Dysfunction and Disrupted Cholesterol Homeostasis (submitted)

Yanjun Liu

Poster: B-392

Constraint-based modelling of macrophages with Gaucher disease



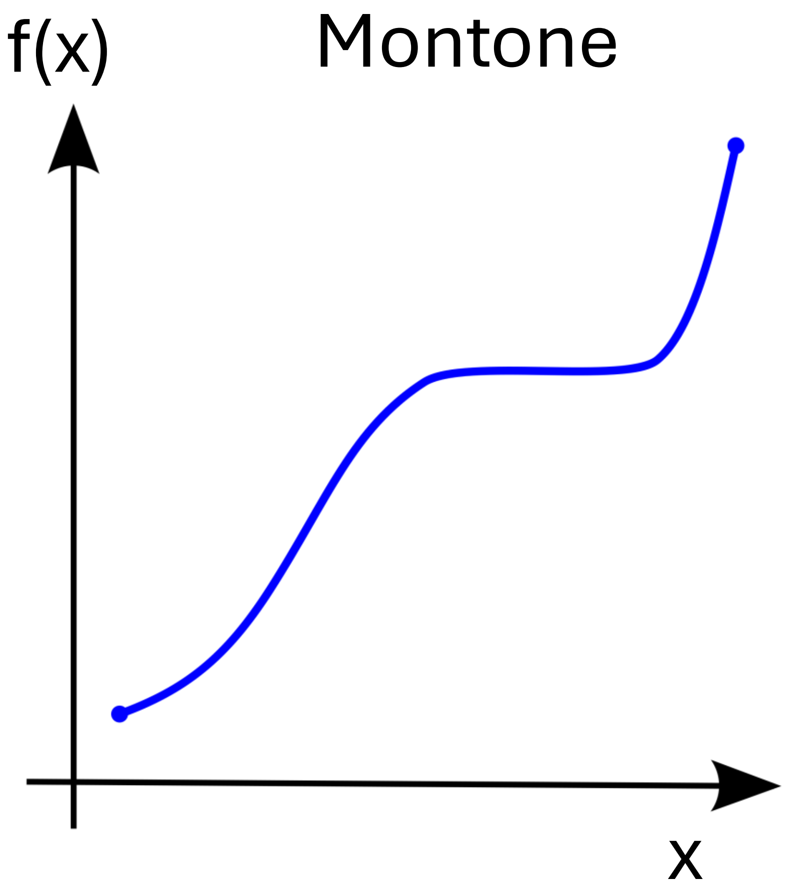
Predicted Gaucher reporter metabolites compared with literature

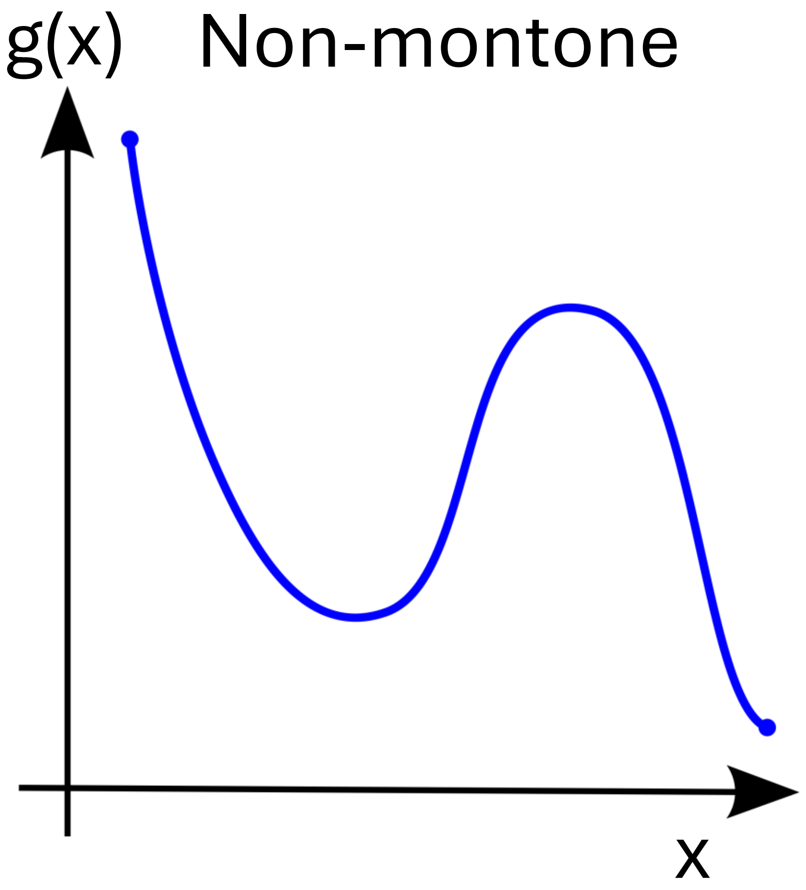
Increase(direct evidence)
Increase(Indirect evidence)
No data available
Decrease(direct evidence)
Decrease(Indirect evidence)

Yanjun Liu
Poster: B-392

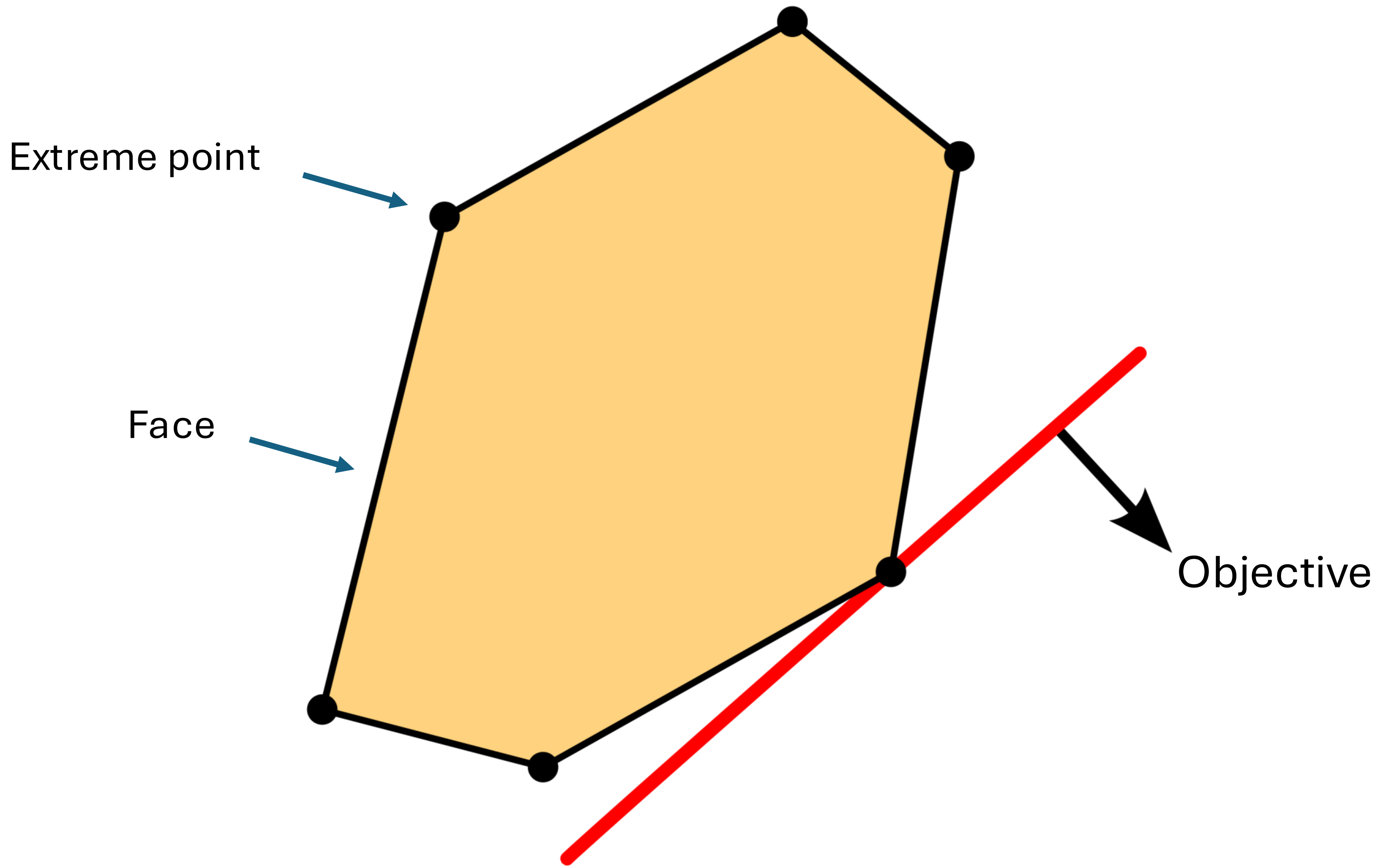
👍 Thermodynamically feasible nonequilibrium steady state

🤔 + kinetics ?

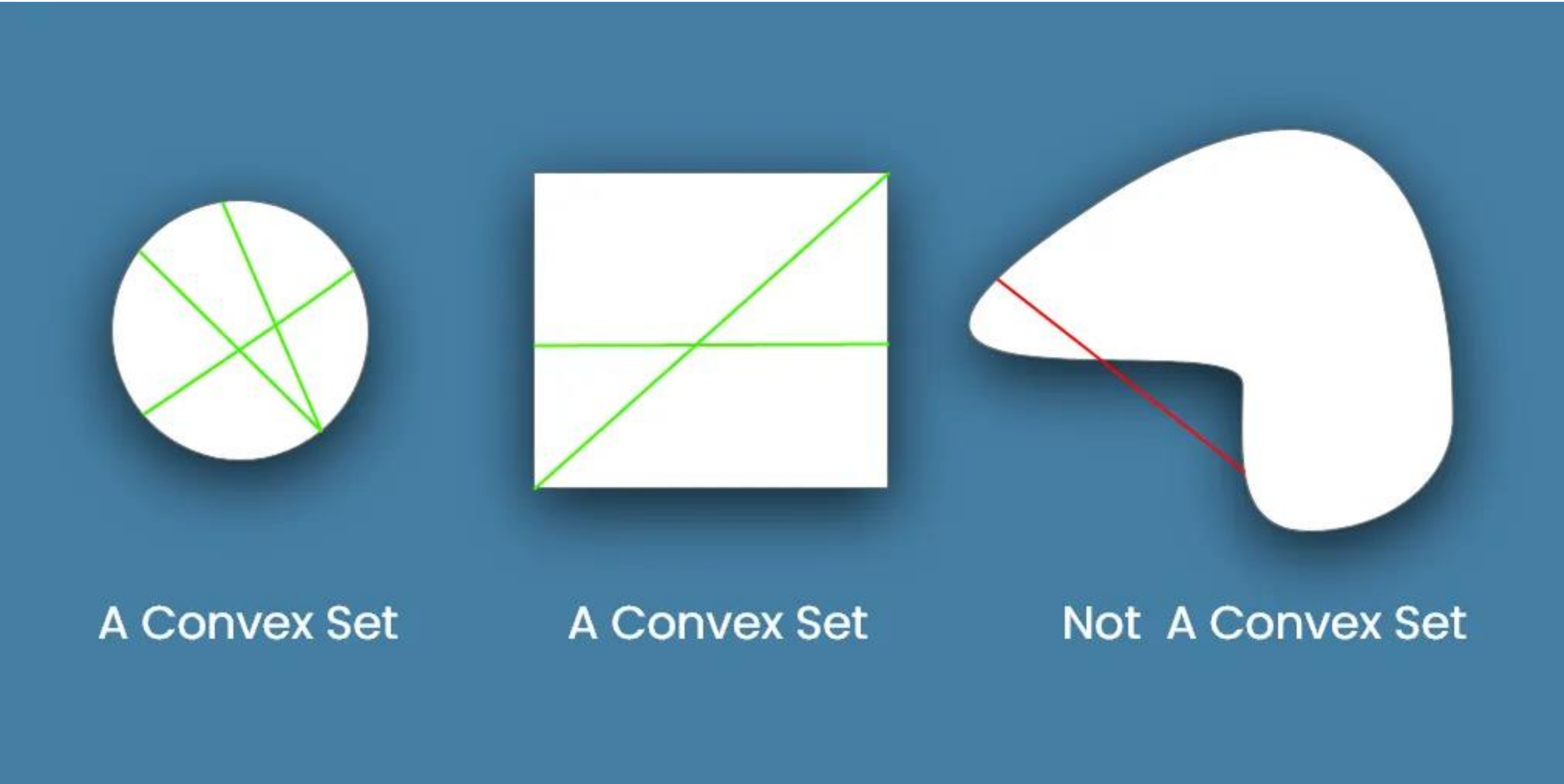




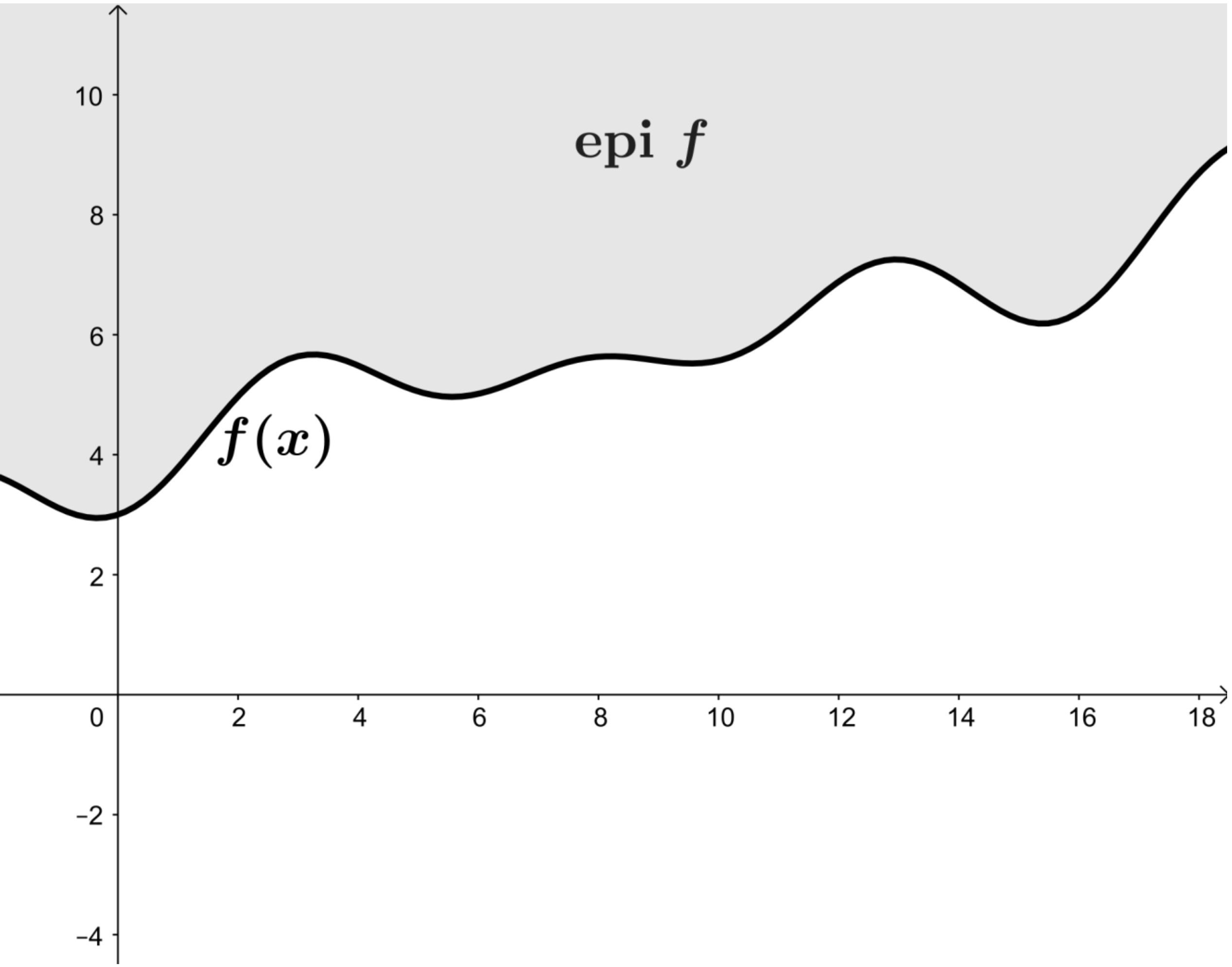
Linear optimisation: linear constraints & linear objective

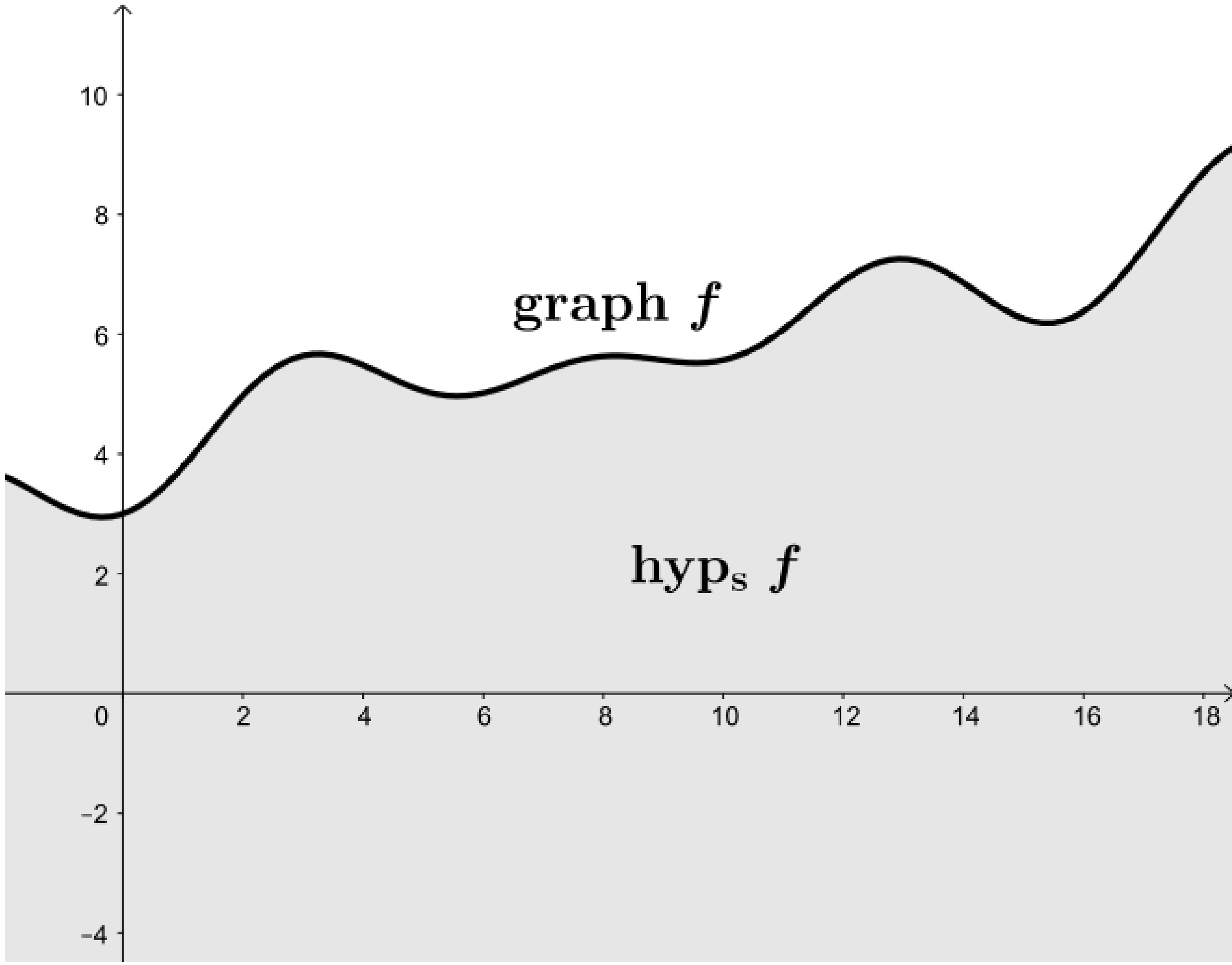


Polyhedral vs non-polyhedral sets, convex vs non-convex sets

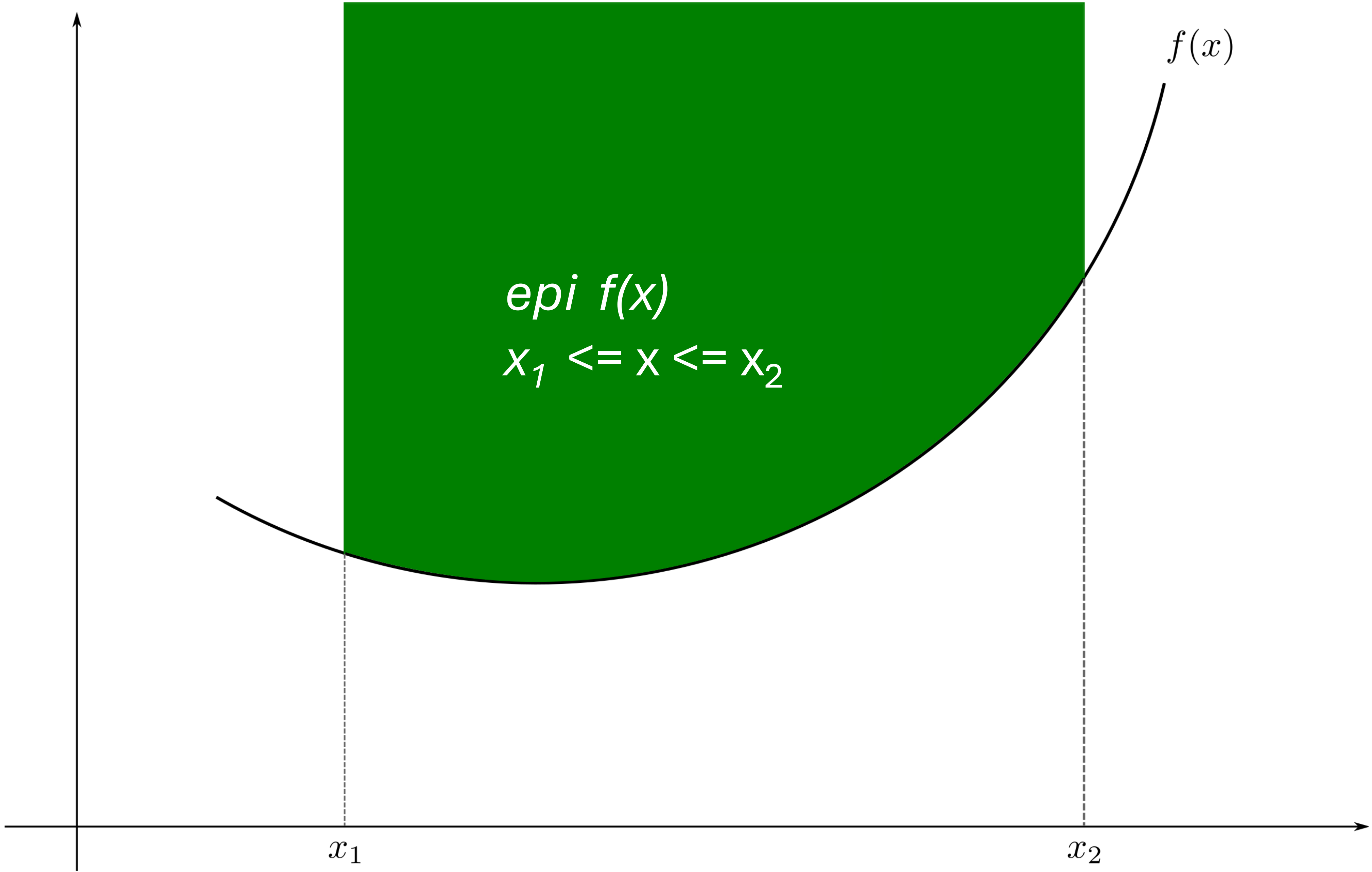


Epigraph versus hypograph



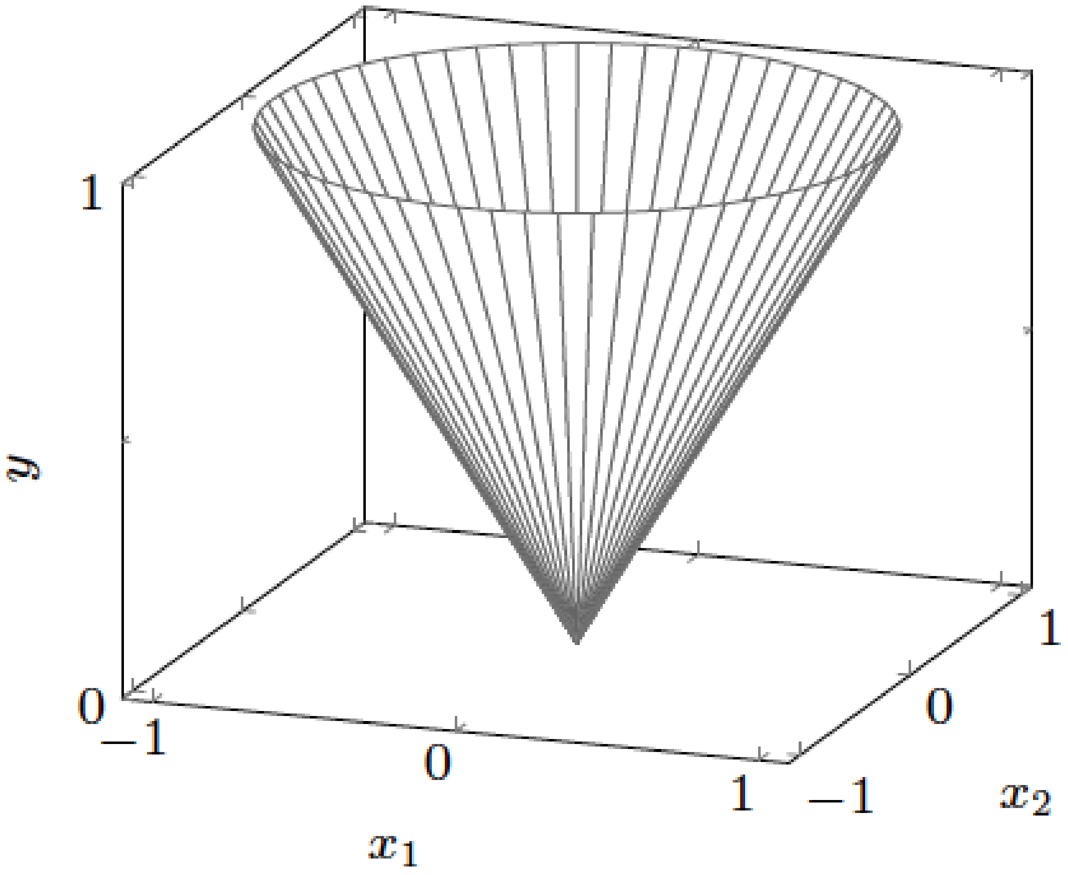


convex function ⇔ epigraph is convex



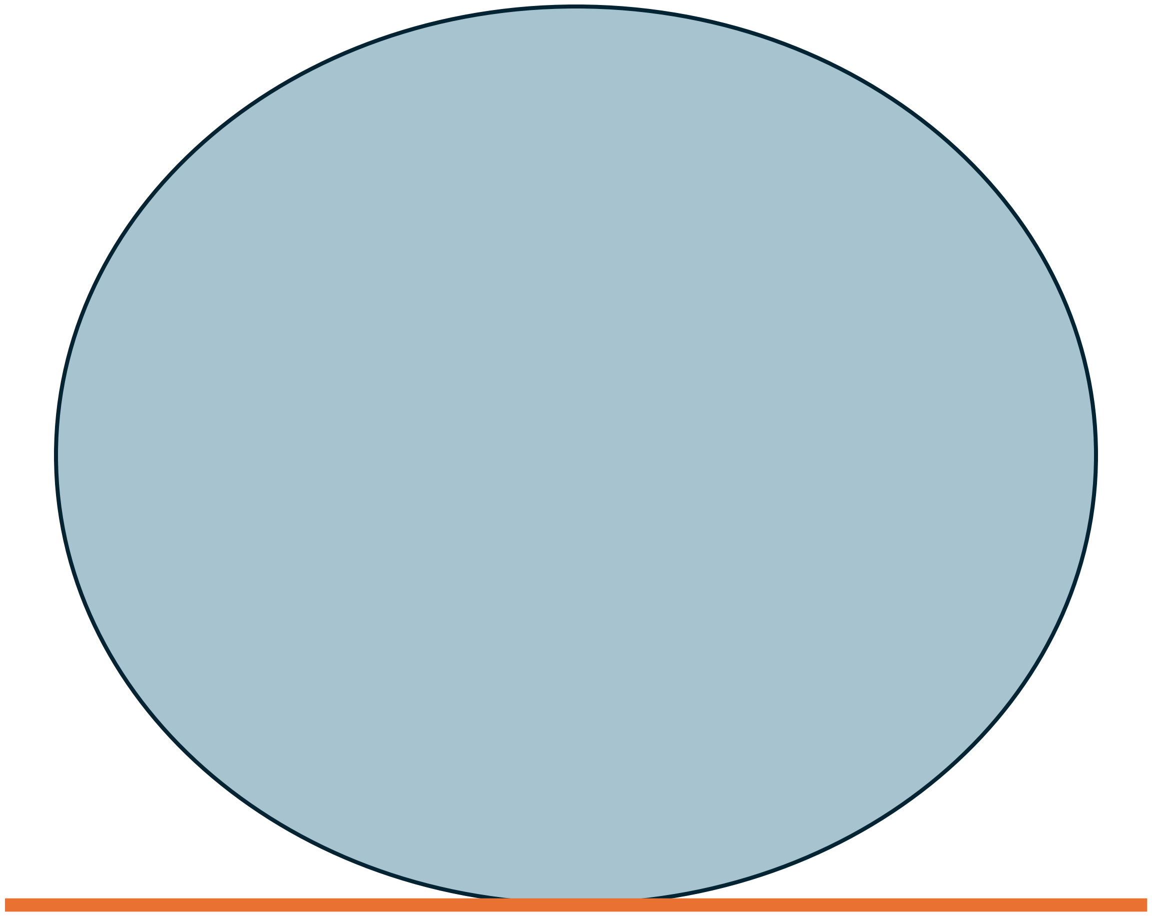
Convex cone, e.g., Euclidean cone

$$K = \{(x, y) \in \mathbf{R}^{m-1} \times \mathbf{R} \mid \|x\| \le y\}$$

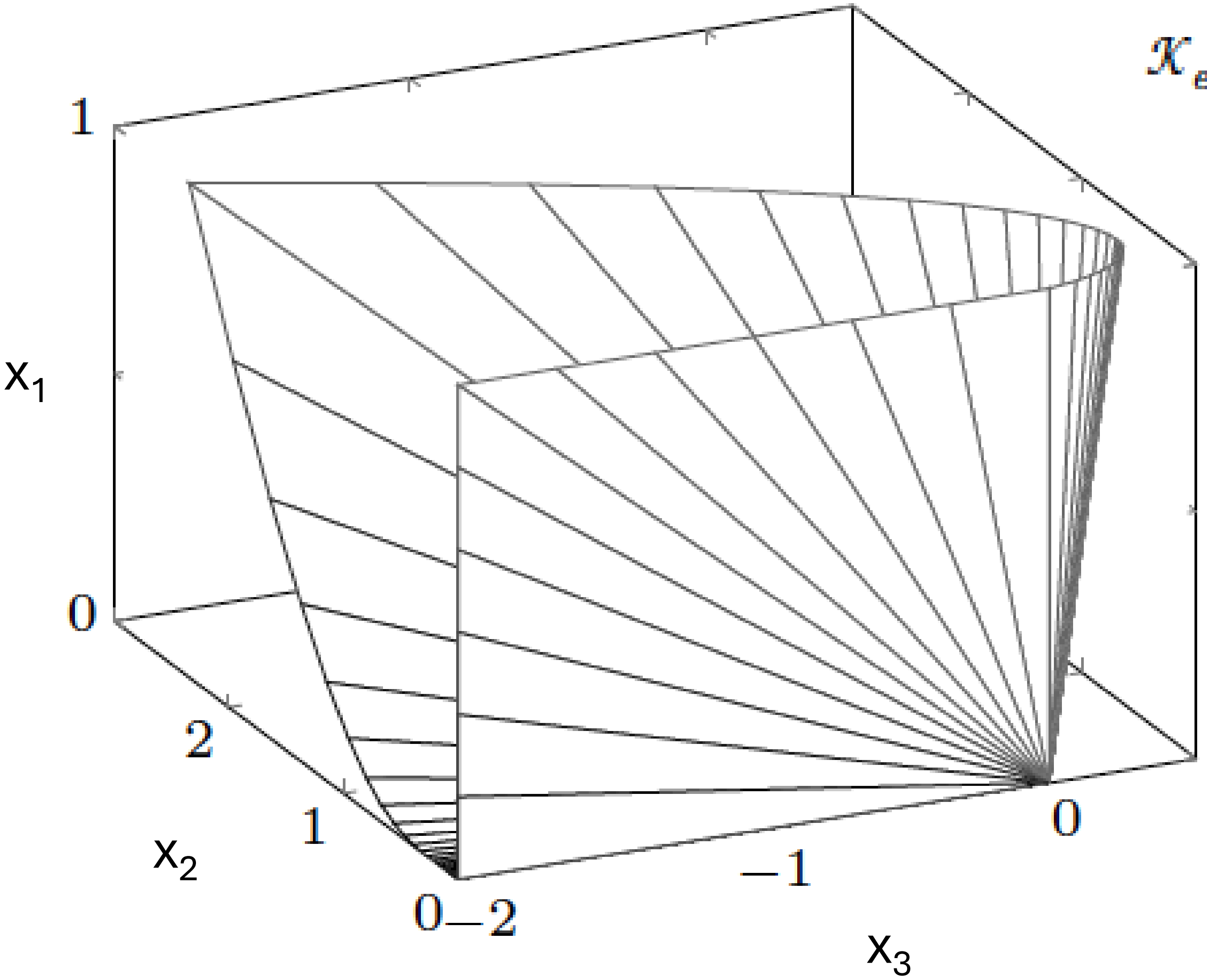


A. Ben-Tal and A. Nemirovski, Lectures on Modern Convex Optimization. Analysis, Algorithms, and Engineering Applications, (2001).

Conic optimisation: cone constraints & linear objective

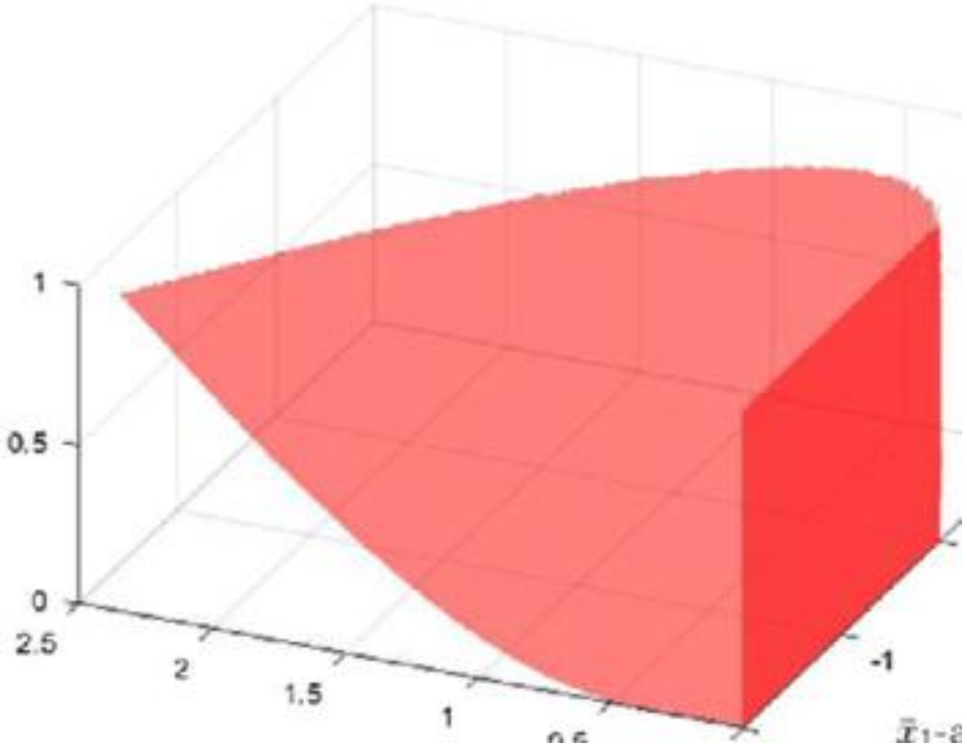


Convex cone, e.g., Exponential cone



$$\mathcal{K}_{exp} := \left\{ (x_1, x_2, x_3) \mid x_1 \geq x_2 \exp\left(\frac{x_3}{x_2}\right), x_1, x_2 > 0 \right\}$$

$$\Leftrightarrow \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} \in \mathcal{K}_{exp}.$$



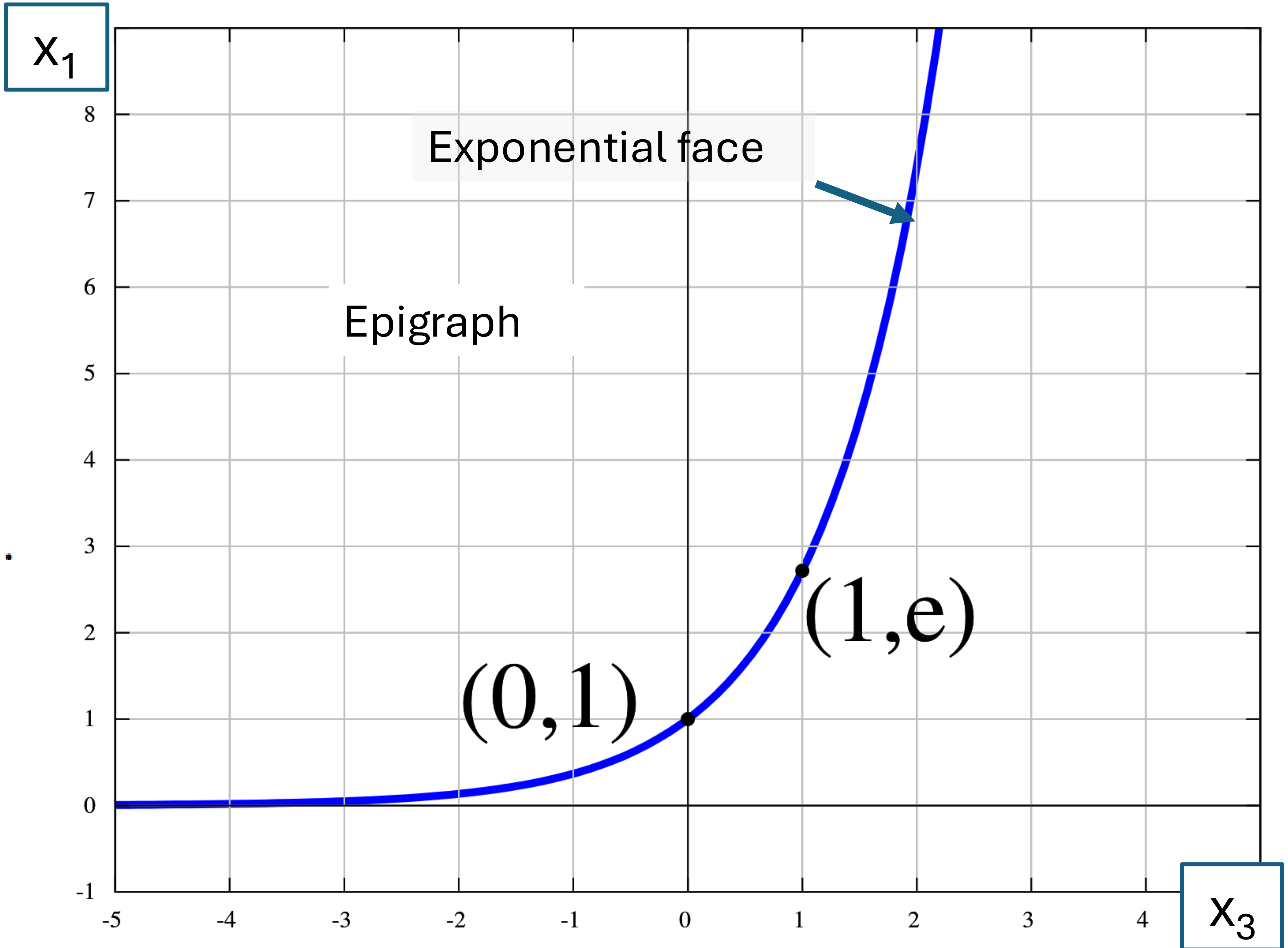
Yurii Nesterov, Arkadii Nemirovskii, Interior-Point Polynomial Algorithms in Convex Programming, 1994.

Epigraph of exponential function is a 2D slice of an exponential cone

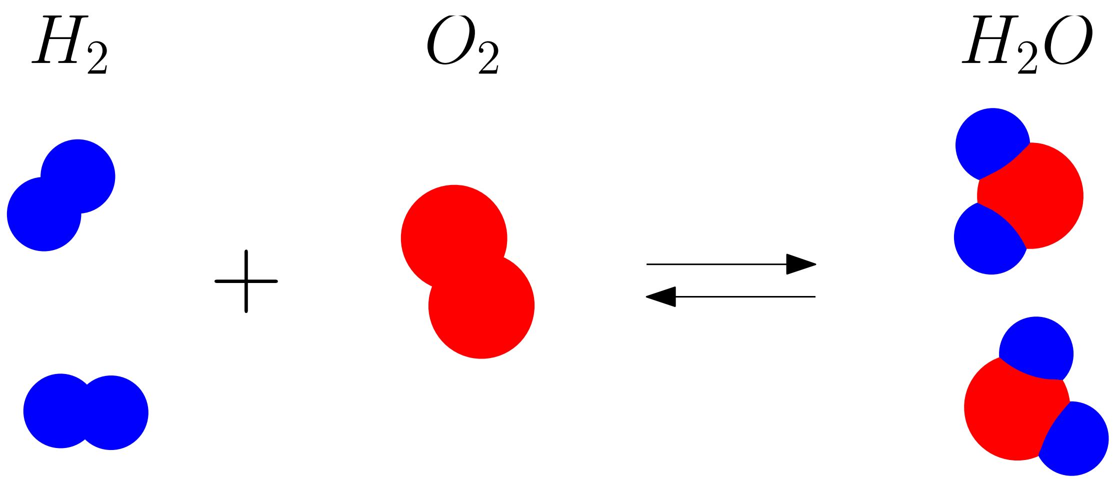
$$\begin{pmatrix} x_1 \\ 1 \\ x_3 \end{pmatrix} \in \mathcal{K}_{exp} \Leftrightarrow$$

$$x_1 \geq \exp(x_3), x_1 > 0.$$

$x_2 = 1$



Matrix-vector formulation of elementary kinetics



$$v_{net}(c, k_f, k_r) := v_f(c \mid k_f) - v_r(c \mid k_r)$$

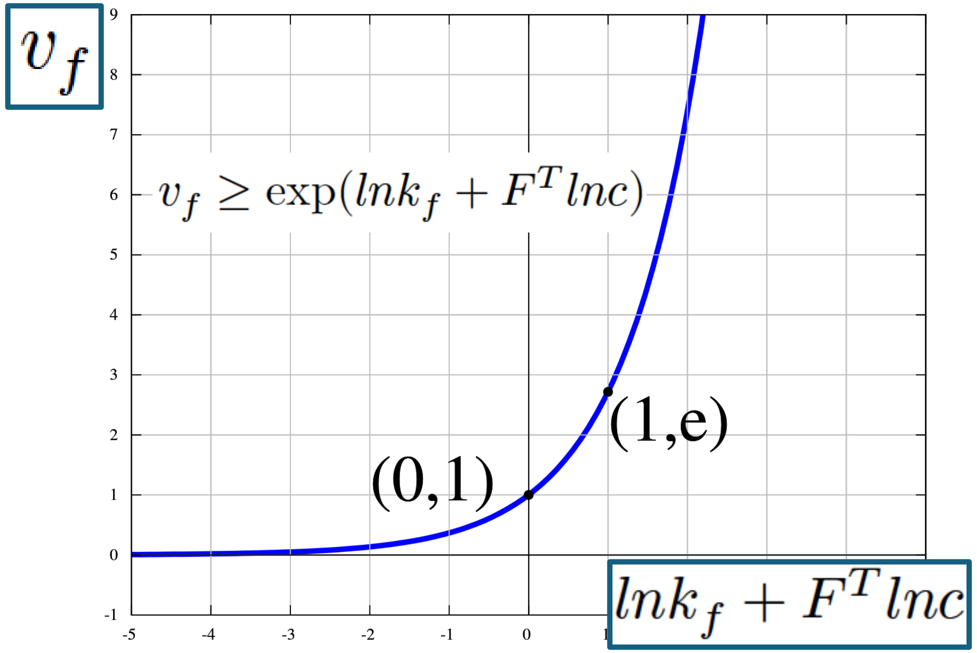
$$N \in \mathbb{Z}^{m \times n} = -F + R$$

$$\begin{aligned} v_{f\mathrm{j}}(c \mid k_{f\mathrm{j}}) &:= k_{f\mathrm{j}} \prod c^{F_{\mathrm{i,j}}} \\ v_{r\mathrm{j}}(c \mid k_{r\mathrm{j}}) &:= k_{r\mathrm{j}} \prod c^{R_{\mathrm{i,j}}} \end{aligned}$$

$$\begin{aligned} v_f(c \mid k_f) &= \exp(\ln(k_f) + F^T \cdot \ln(c)) \\ v_r(c \mid k_r) &= \exp(\ln(k_r) + R^T \cdot \ln(c)), \end{aligned}$$

Variational kinetics: kinetic modelling with optimisation methods

$$
\begin{aligned}
lnk_f &:= \ln(k_f) \\
lnk_r &:= \ln(k_r) \\
lnc &:= \ln(c)
\end{aligned}
$$



$$
\min_{v_f, v_r, w, lnc} \quad c_{v_f}^T \cdot v_f + c_{v_r}^T \cdot v_r + c_{lnc}^T \cdot lnc
$$

$$
\text{s.t.} \quad N \cdot (v_f - v_r) + B \cdot w = 0
$$

$$
\begin{pmatrix} v_f \\ 1 \\ F^T lnc + lnk_f \end{pmatrix} \in \mathcal{K}_{exp}^n \iff v_f \geq \exp\left(F^T lnc + lnk_f\right)
$$

$$
\begin{pmatrix} v_r \\ 1 \\ R^T lnc + lnk_r \end{pmatrix} \in \mathcal{K}_{exp}^n \iff v_r \geq \exp\left(R^T lnc + lnk_r\right)
$$

$$\min \quad c_{v_f}^T \cdot v_f + c_{v_r}^T \cdot v_r + c_{lnc}^T \cdot lnc \ldots$$

Optimise fluxes and logarithmic concentrations to exponential faces

$$+c_c^T \cdot c \ldots$$

Optimise concentrations to the exponential faces

$$+c_{e_f}^T \cdot e_f + c_{e_r}^T \cdot e_r + c_{e_c}^T \cdot e_c \ldots$$

Maximise entropy of fluxes and concentrations

$$+c_{t_v} \cdot t_v + c_w \cdot t_w + c_{t_{lnk_f}} \cdot t_{lnk_f} \ldots$$

$$+c_{t_{lnk_r}} \cdot t_{lnk_r} + c_{t_{lnc}} \cdot t_{lnc} + c_{t_{u^\circ}} \cdot t_{u^\circ} \ldots$$

Minimise quadratic penalties from given mean (+/- variance) in net flux, logarithmic elementary kinetic parameters, logarithmic concentration, standard Gibbs energy.

$$+c_{t_r} \cdot t_r$$

Regularised mass balance

$$\text{s.t.} \quad N \cdot (v_f - v_r) + r + B \cdot w = 0$$

Thermodynamically feasible kinetic parameters

$$lnk_f - lnk_r + N^T \cdot u^\circ = 0$$

Moiety conservation

$$L \cdot c = L \cdot c(0)$$

$$\begin{pmatrix} v_f \\ 1 \\ F^T \cdot lnc + lnk_f \end{pmatrix} \in \mathcal{K}_{exp}^n, \quad \begin{pmatrix} v_r \\ 1 \\ R^T \cdot lnc + lnk_r \end{pmatrix} \in \mathcal{K}_{exp}^n, \quad \begin{pmatrix} c \\ 1 \\ lnc \end{pmatrix} \in \mathcal{K}_{exp}^m$$

Exponential cones for elementary reaction kinetics

$$\begin{pmatrix} 1 \\ v_f \\ -e_f \end{pmatrix} \in \mathcal{K}_{exp}^n, \quad \begin{pmatrix} 1 \\ v_r \\ -e_r \end{pmatrix} \in \mathcal{K}_{exp}^n, \quad \begin{pmatrix} 1 \\ c \\ -e_c \end{pmatrix} \in \mathcal{K}_{exp}^m$$

Exponential cones for entropy of forward & reverse flux, and concentration

,

$$\begin{pmatrix} t_v \\ 1 \\ H_v \cdot (v_f - v_r) - h_v \end{pmatrix} \in \mathcal{Q}^{2+n}, \quad \begin{pmatrix} t_w \\ 1 \\ H_w \cdot (w - h_w) \end{pmatrix} \in \mathcal{Q}^{2+k},$$

Quadratic cones for integration of mean (+/- variance) in internal and external fluxes

$$\begin{pmatrix} t_{lnk_f} \\ 1 \\ H_{lnk_f} \cdot (lnk_f - h_{lnk_f}) \end{pmatrix} \in \mathcal{Q}^{2+n}, \quad \begin{pmatrix} t_{lnk_r} \\ 1 \\ H_{lnk_r} \cdot (lnk_r - h_{lnk_r}) \end{pmatrix} \in \mathcal{Q}^{2+n},$$

Quadratic cones for integration of mean (+/- variance) in logarithmic kinetic param

$$\begin{pmatrix} t_{lnc} \\ 1 \\ H_{lnc} \cdot (lnc - h_{lnc}) \end{pmatrix} \in \mathcal{Q}^{2+m}, \quad \begin{pmatrix} t_{u^\circ} \\ 1 \\ H_{u^\circ} \cdot (u^\circ - h_{u^\circ}) \end{pmatrix} \mathcal{Q}^{2+m}$$

Quadratic cones for integration of mean (+/- variance) in concentrations & standard chemical potential

$$\begin{pmatrix} t_r \\ 1 \\ H_r \cdot r \end{pmatrix} \in \mathcal{Q}^{2+m}.$$

Quadratic cones for regularisation of mass balance

Variational convenience kinetics: numerical results

Test model: genome-scale model of dopaminergic neuronal metabolism*.

Metabolites	1244
rank(S)	1161
External reactions	205
Internal reactions	1710
Genes	1212

Constraints : 12199
Cones : 9332
Variables : 34105
Conically constrained variables : 33900

Optimizer time: 2.34 seconds!

Total time ~14 seconds, construct, solve, numerically evaluate, etc.

Variational kinetics (unpublished)

* = Preciat G. et. al., Comm. Biol. (to appear) https://doi.org/10.1101/2021.06.30.450562

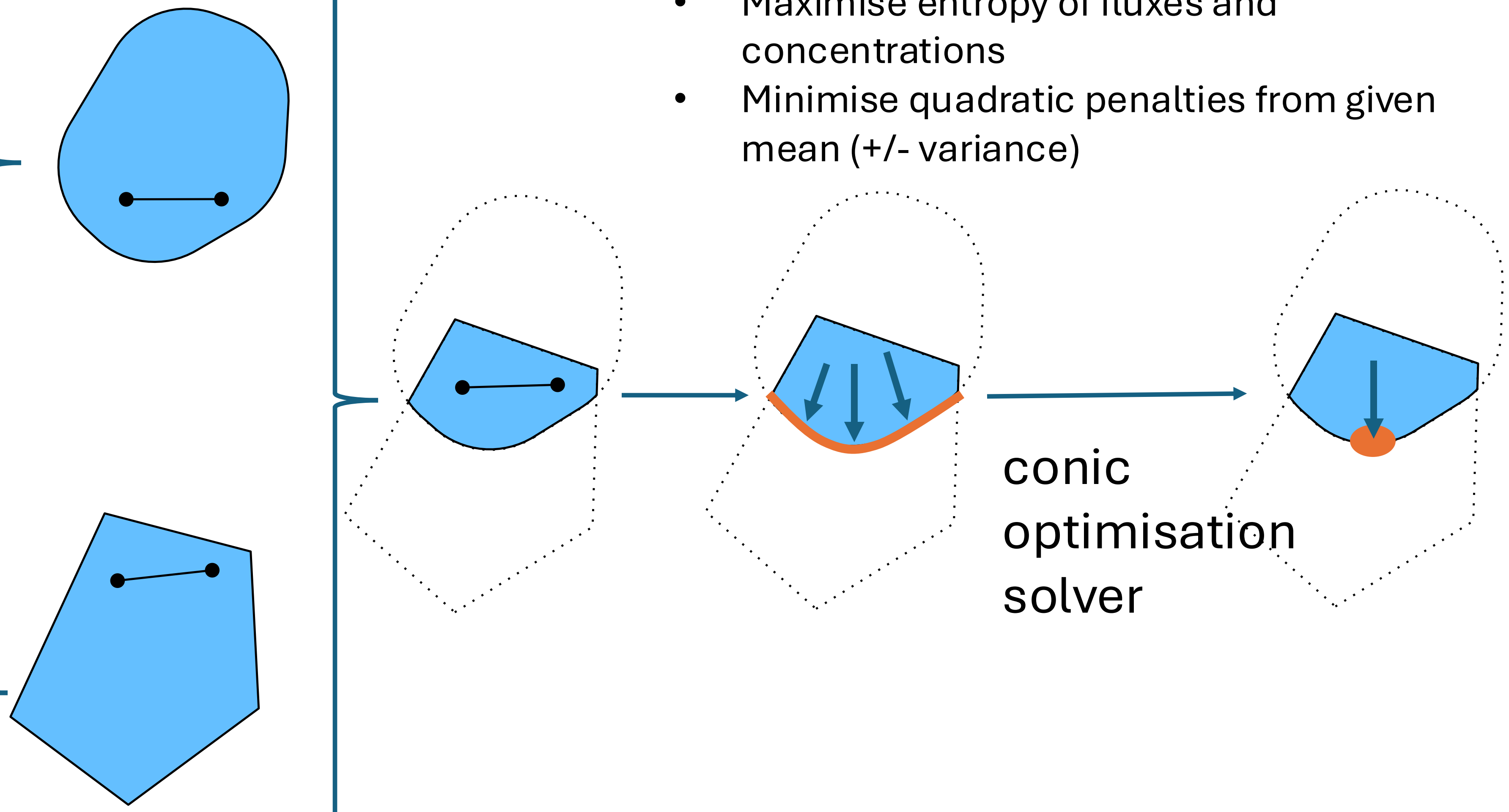
Variational kinetics: a variational formulation of reaction kinetics

Exponential cone epigraphs
- (elementary) reaction kinetics
- entropy of forward & reverse fluxes, and concentration
- linear and logarithmic concentrations

Quadratic cones for data integration (mean +/- variance)
- internal and external fluxes
- logarithmic elementary kinetic param
- logarithmic concentrations
- standard chemical potentials

Polyhedral convex constraints
- Mass balance
- Thermodynamically feasible kinetic parameters
- Moiety conservation

- Optimise fluxes, concentrations & elementary kinetic parameters to exponential cone boundaries
- Maximise entropy of fluxes and concentrations
- Minimise quadratic penalties from given mean (+/- variance)



Convenience kinetics

Net reaction rate

Enzyme concentration

Metabolite concentration

Forward and reverse stoichiometric coefficients

$$v_j(c \mid k_f^{cat}, k_r^{cat}, k_M) := \frac{E_j \left(k_{f,j}^{cat} \left(\prod_{i=1}^{m} \left(\frac{c_i}{k_{M,i}} \right)^{F_{i,j}} \right) - k_{r,j}^{cat} \left(\prod_{i=1}^{m} \left(\frac{c_i}{k_{M,i}} \right)^{R_{i,j}} \right) \right)}{\prod_{i=1}^{m} \left(\sum_{k=0}^{F_{i,j}} \left(\frac{c_i}{k_{M,i}} \right)^{k} \right) + \prod_{i=1}^{m} \left(\sum_{k=0}^{R_{i,j}} \left(\frac{c_i}{k_{M,i}} \right)^{k} \right) - 1}$$

Catalytic constants

Michaelis constants

- rapid-equilibrium random-order enzyme mechanism
- works for any stoichiometric coefficient
- we assume {-1,0,1}

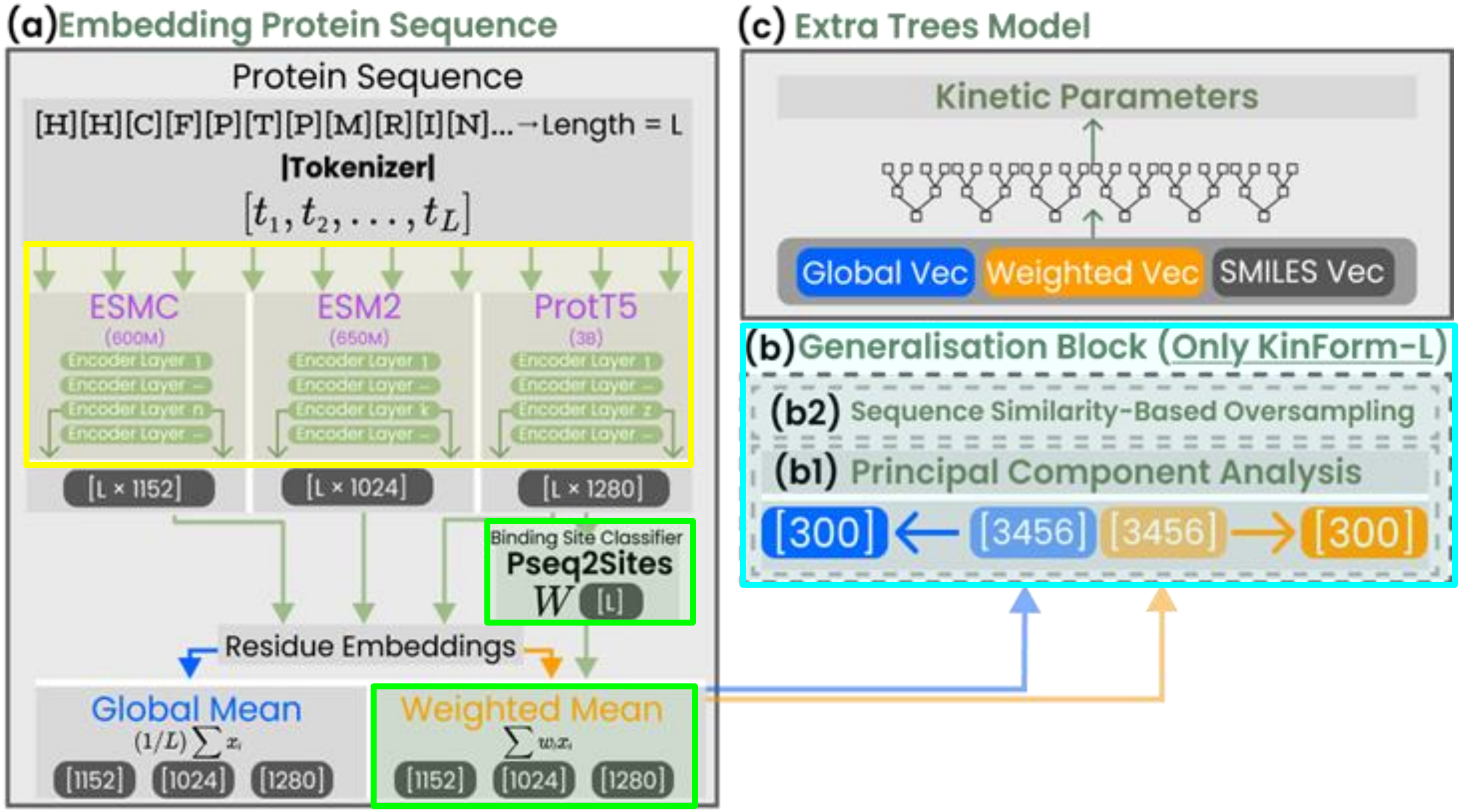
Liebermeister W, Klipp E. Bringing metabolic networks to life: convenience rate law and thermodynamic constraints. Theor Biol Med Model. 2006 Dec 15;3:41. doi: 10.1186/1742-4682-3-41.

KinForm: **Kin**etics-**I**nformed **F**eature-**O**ptimized **M**odels for enzyme kinetic parameter prediction

improved enzyme kinetic prediction by enhancing protein representations using intermediate transformer layer selection, binding-site weighting and dimensionality reduction.

Saleh Alwer
Poster: B-295

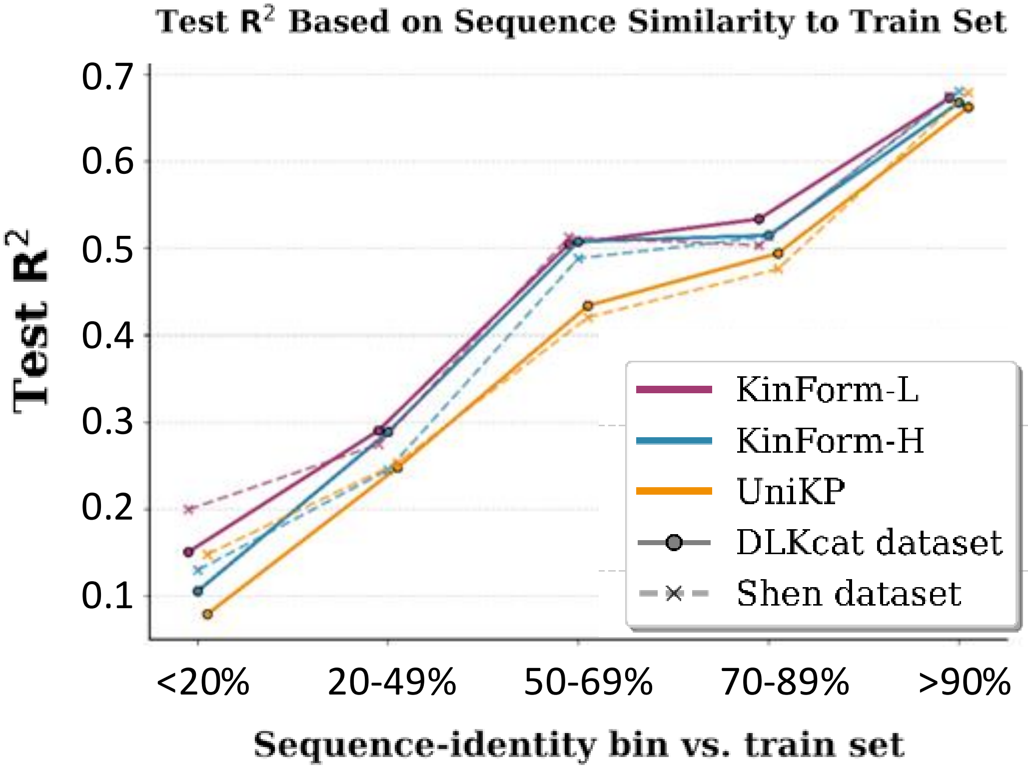
Method



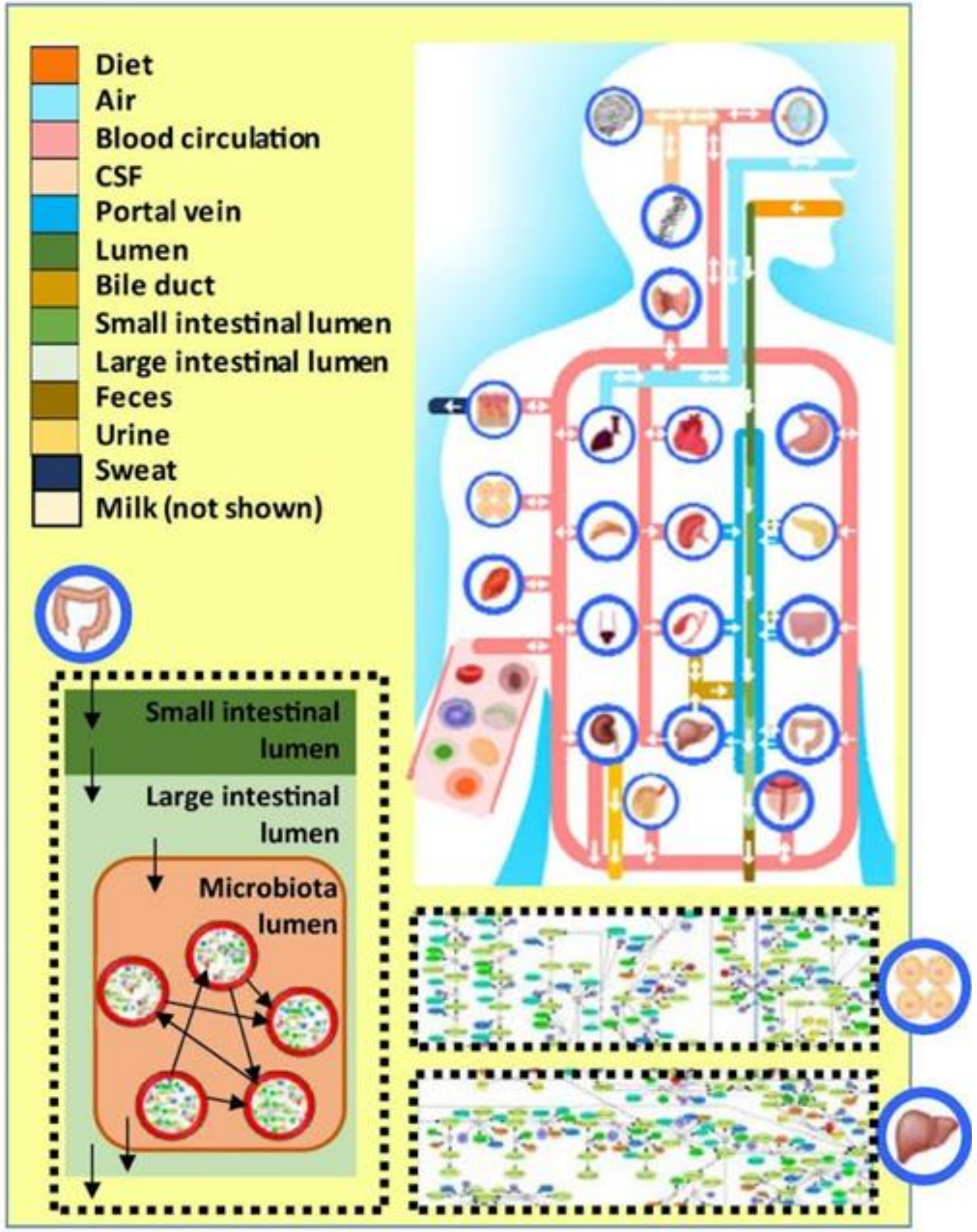
Alwer et. al. (2025) https://arxiv.org/abs/2507.14639

Result

KinForm outperforms the UniKP baseline model, especially on data-points with low-similarity to the training data.



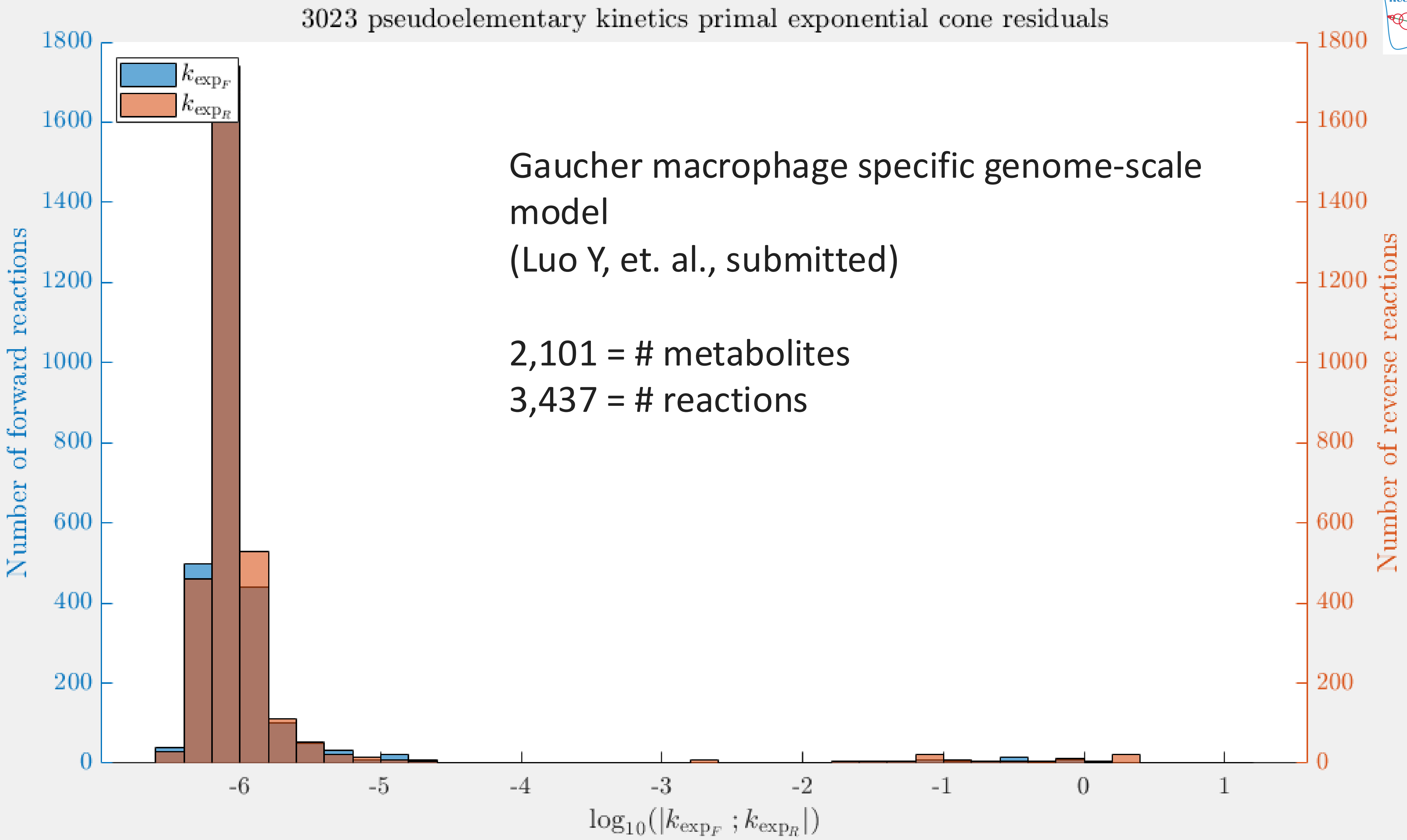
Is variational kinetics a scalable approach?



problem	model	stat	origStat	time (sec)
"LP"	"Harvey"	1	"OPTIMAL"	1.9012
"QP"	"Harvey"	1	"OPTIMAL"	11.479
"EP"	"Harvey"	1	"OPTIMAL"	54.092
"VK"	"Harvey"	1	"OPTIMAL"	196.47
"VCK"	"Harvey"	1	"OPTIMAL"	239.08

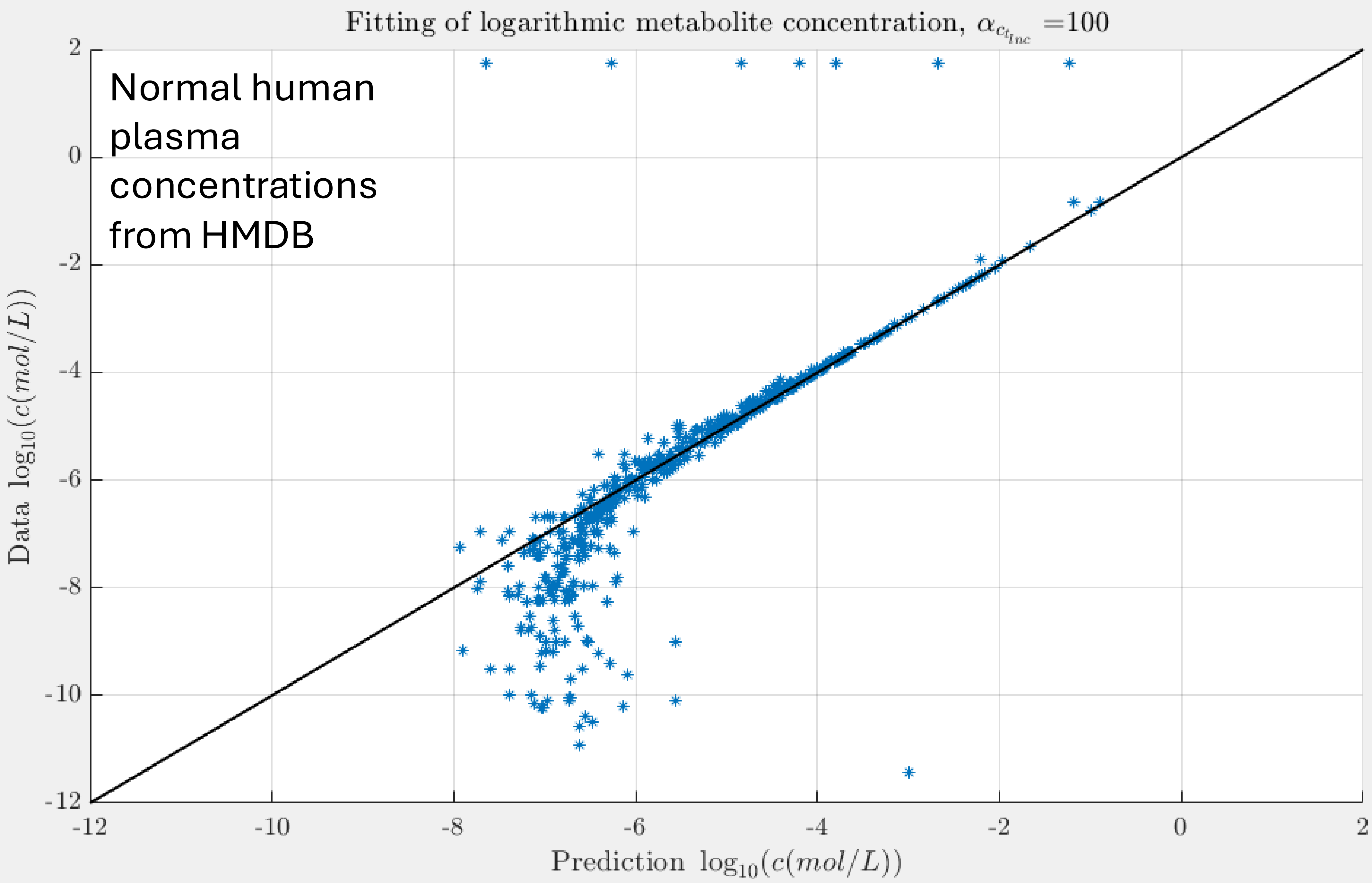
```
MOSEK Version 10.2.5 (Build date: 2024-9-17 12:12:35)
Copyright (c) MOSEK ApS, Denmark WWW: mosek.com
Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : CONIC (conic optimization problem)
  Constraints            : 575535
  Affine conic cons.     : 1229562 (4620757 rows)
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 3673203
  Matrix variables       : 0
  Integer variables      : 0
```

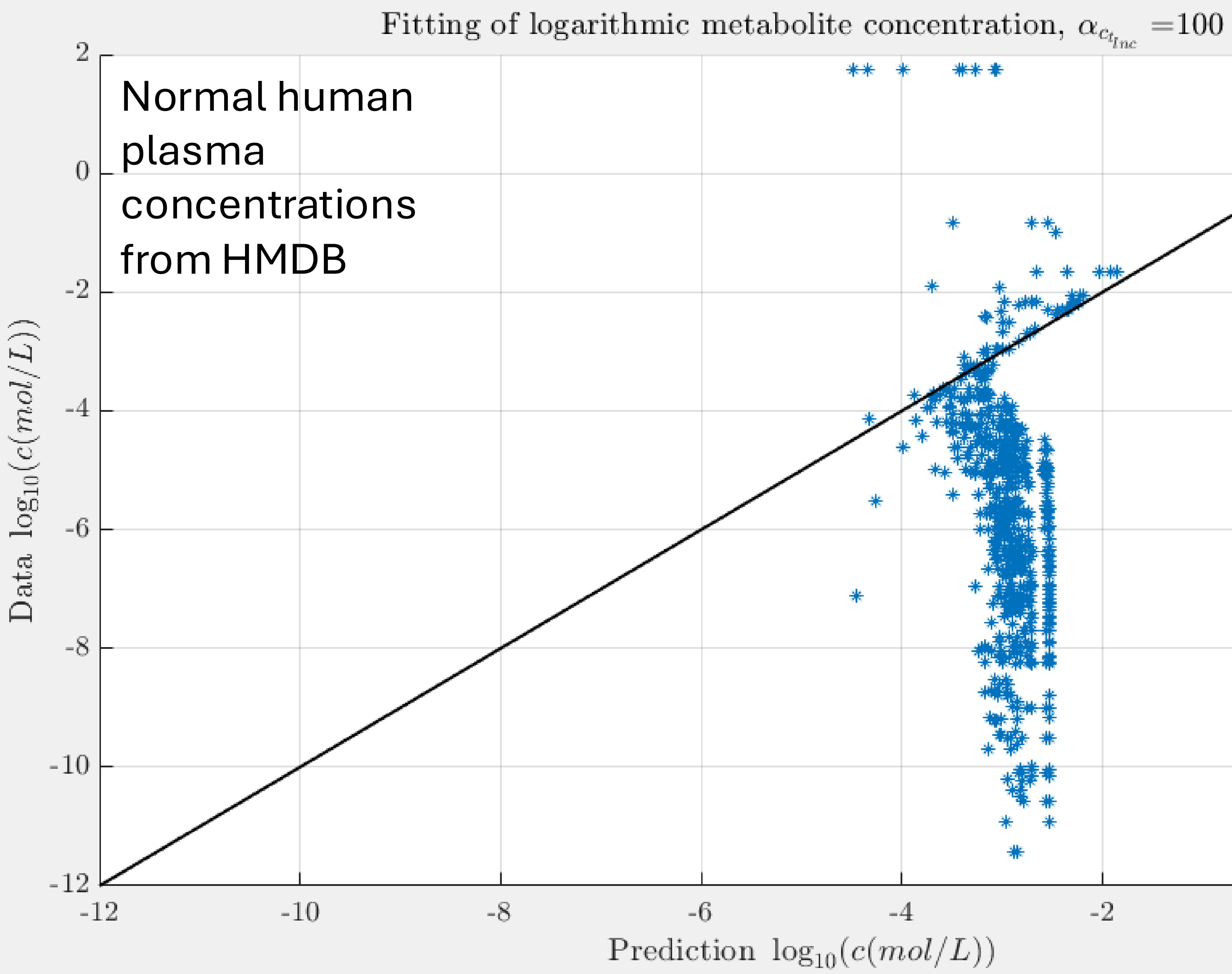
Thiele, I. *et al. Molecular Systems Biology* **16**, 24 (2020).



Gaucher macrophage specific genome-scale model
(Luo Y, et. al., submitted)

2,101 = # metabolites
3,437 = # reactions


Fitting of logarithmic metabolite concentration, $\alpha_{c_{t_{Inc}}}$ =100
Normal human plasma concentrations from HMDB
Data $\log_{10}(c(mol/L))$
Prediction $\log_{10}(c(mol/L))$
2
0
-2
-4
-6
-8
-10
-12
-12
-10
-8
-6
-4
-2
0
2

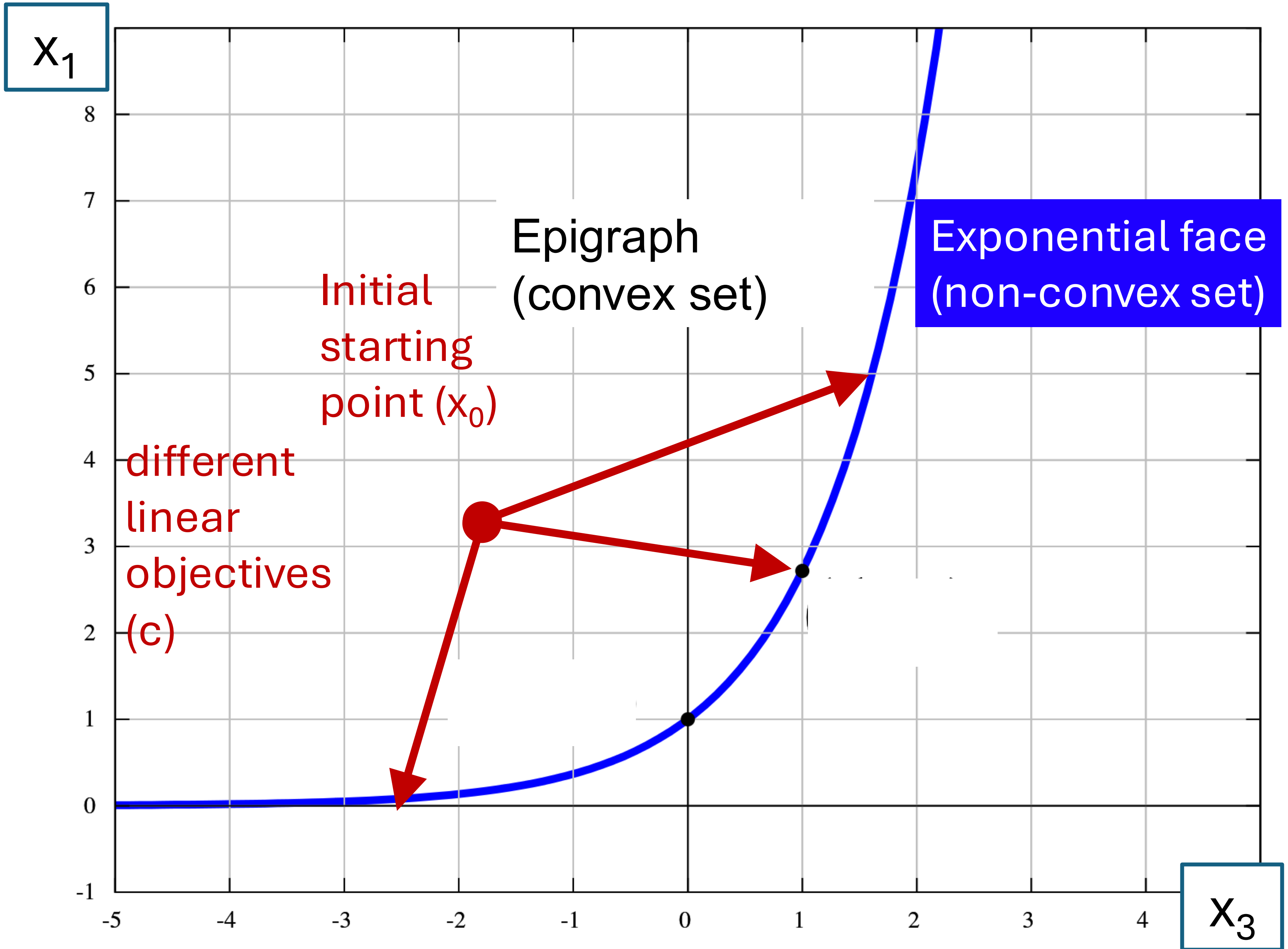

Fitting of logarithmic metabolite concentration, $\alpha_{c_{t_{Inc}}}$ =100
Normal human plasma concentrations from HMDB
Data $\log_{10}(c(mol/L))$
Prediction $\log_{10}(c(mol/L))$
2
0
-2
-4
-6
-8
-10
-12
-12
-10
-8
-6
-4
-2
0
2

2D slice of an exponential cone

$$\min_x \quad c^T x$$
$$\text{s.t.} \quad \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} \in \mathcal{K}_{exp}$$
$$x_2 = 1$$

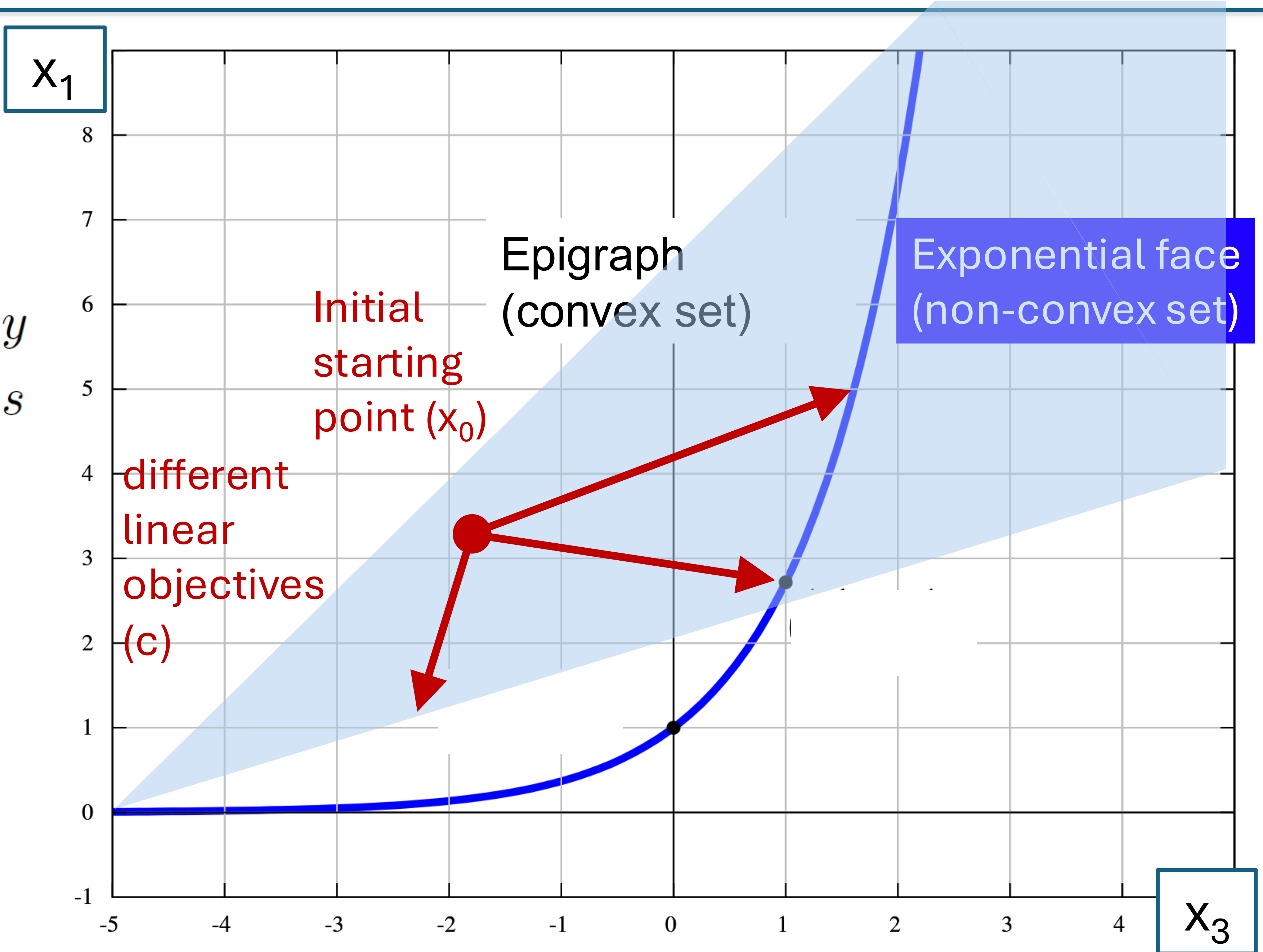
$$\Updownarrow$$

$$\min_x \quad c^T x$$
$$\text{s.t.} \quad x_1 \geq \exp(x_3)$$
$$x_2 = 1$$



2D slice of an exponential cone intersecting with a convex polytope

$$\begin{aligned} \min_{x} \quad & c^T x & \\ \text{s.t.} \quad & A \cdot x \leq b & : y \\ & F \cdot x + g \in \mathcal{K}_{exp} & : s \end{aligned}$$



Convergence of a sequence of conic optimisation problems

$$\begin{pmatrix} F_1 \cdot x + g_1 \\ 1 \\ F_3 \cdot x + g_3 \end{pmatrix} \in \mathcal{K}_{exp}$$

$$\Updownarrow$$

$$(F_1 \cdot x + g_1) \geq \exp(F_3 \cdot x + g_3)$$

$$\Updownarrow$$

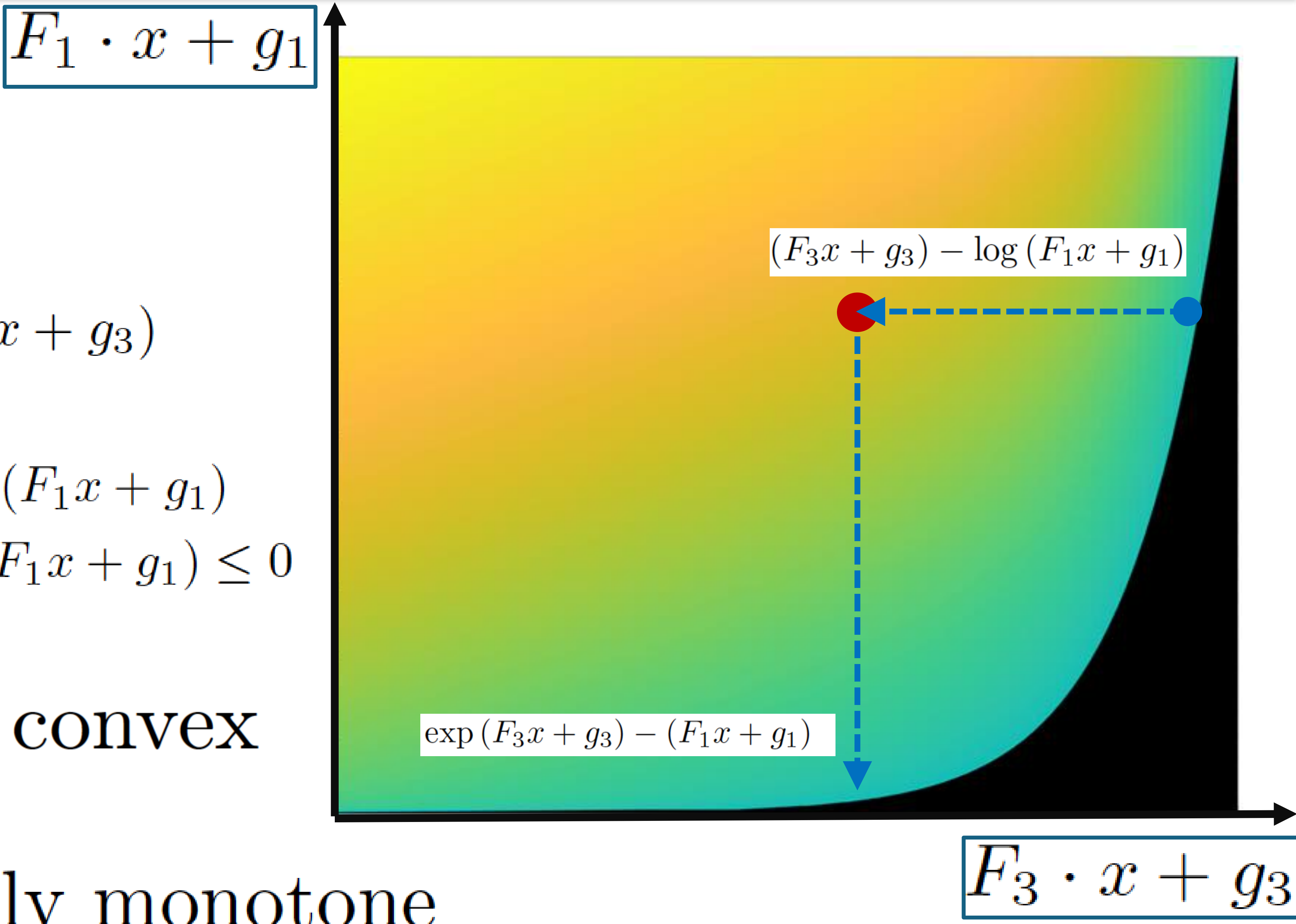
$$\phi(x) := \exp\left(F_3 x + g_3\right) - \left(F_1 x + g_1\right) + \left(F_3 x + g_3\right) - \log\left(F_1 x + g_1\right) \leq 0$$

$$\Updownarrow$$

$\phi(x)$ is strictly convex

$$\Updownarrow$$

$\nabla_x \phi(x)$ is strictly monotone



Convergence of a sequence of conic optimisation problems

$$\begin{pmatrix} F_1 \cdot x + g_1 \\ 1 \\ F_3 \cdot x + g_3 \end{pmatrix} \in \mathcal{K}_{exp}$$

$$\Updownarrow$$

$$(F_1 \cdot x + g_1) \geq \exp(F_3 \cdot x + g_3)$$

$$\Updownarrow$$

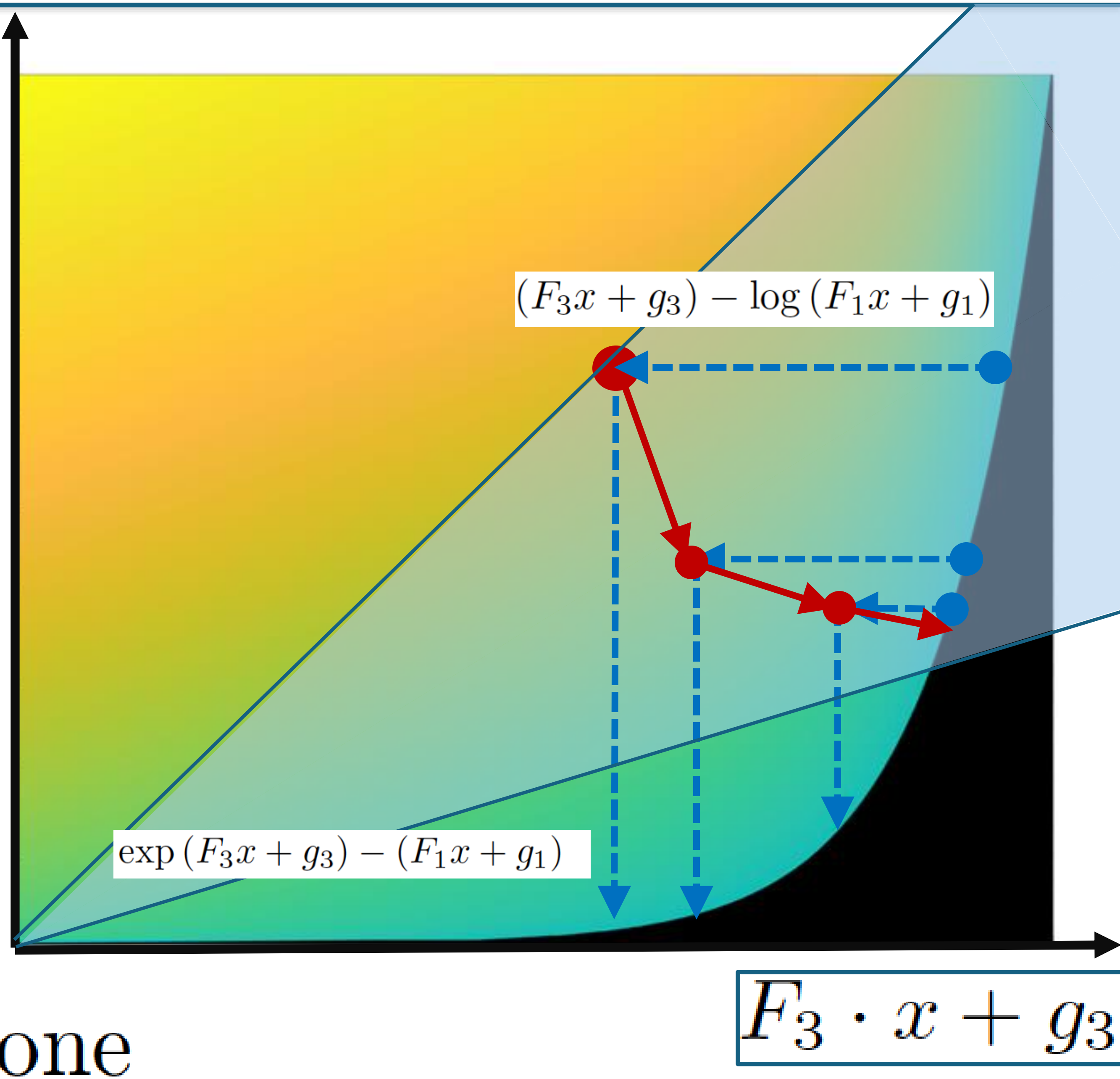
$$\phi(x) := \exp\left(F_3 x + g_3\right) - \left(F_1 x + g_1\right) + \left(F_3 x + g_3\right) - \log\left(F_1 x + g_1\right) \leq 0$$

$$\Updownarrow$$

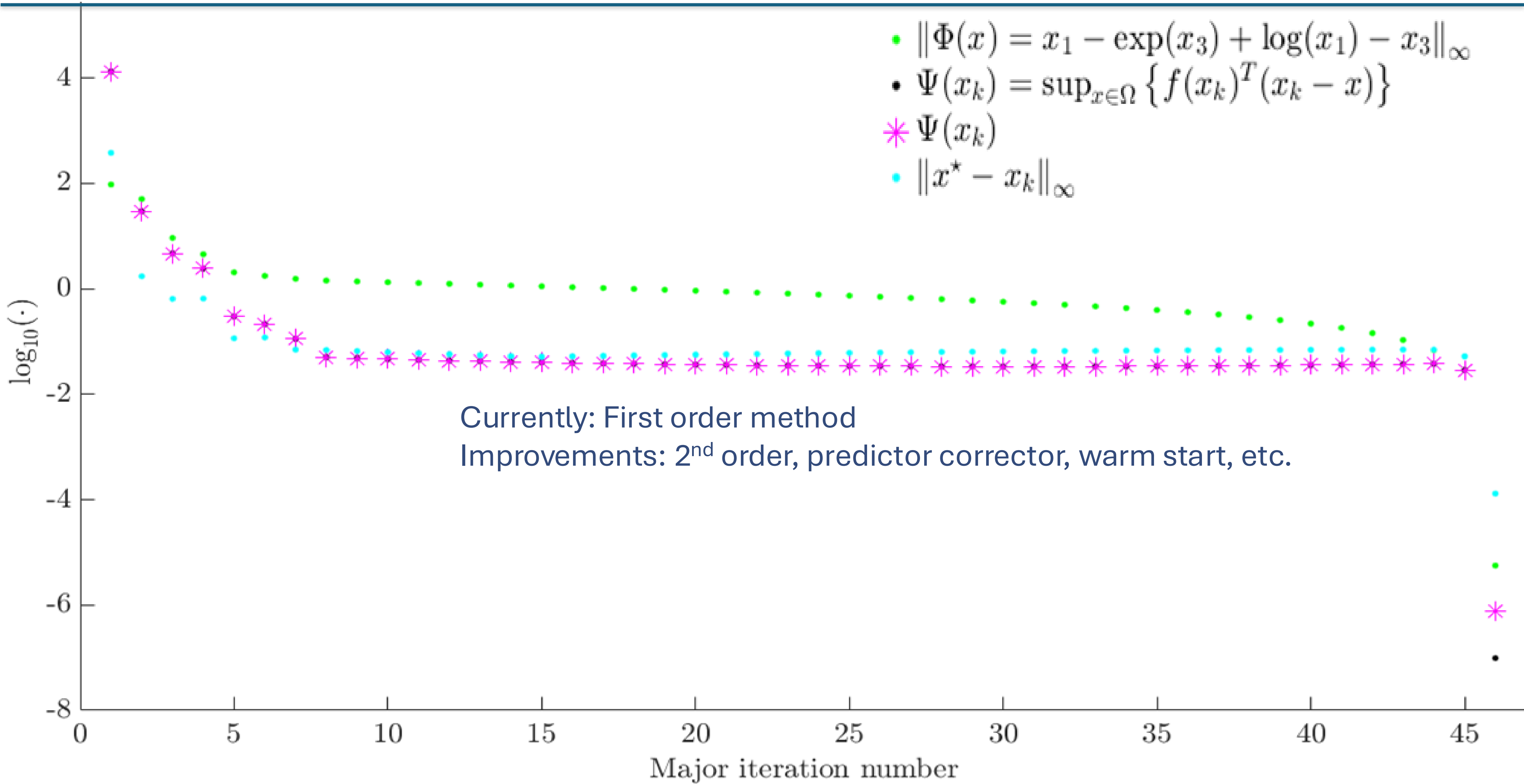
$\phi(x)$ is strictly convex

$$\Updownarrow$$

$\nabla_x \phi(x)$ is strictly monotone



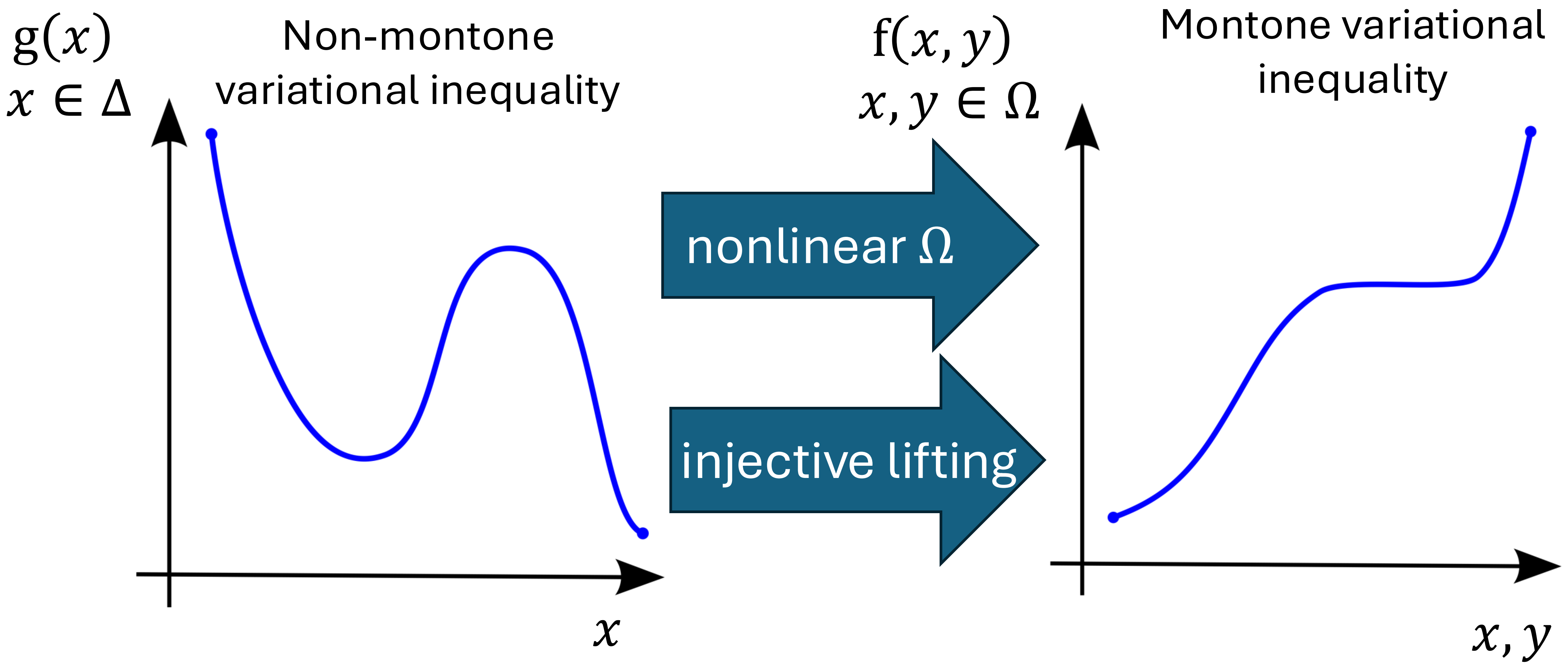
Convergence of a sequence of conic optimisation problems



Currently: First order method

Improvements: 2nd order, predictor corrector, warm start, etc.

Monotonicity can depend on feasible set and dimension

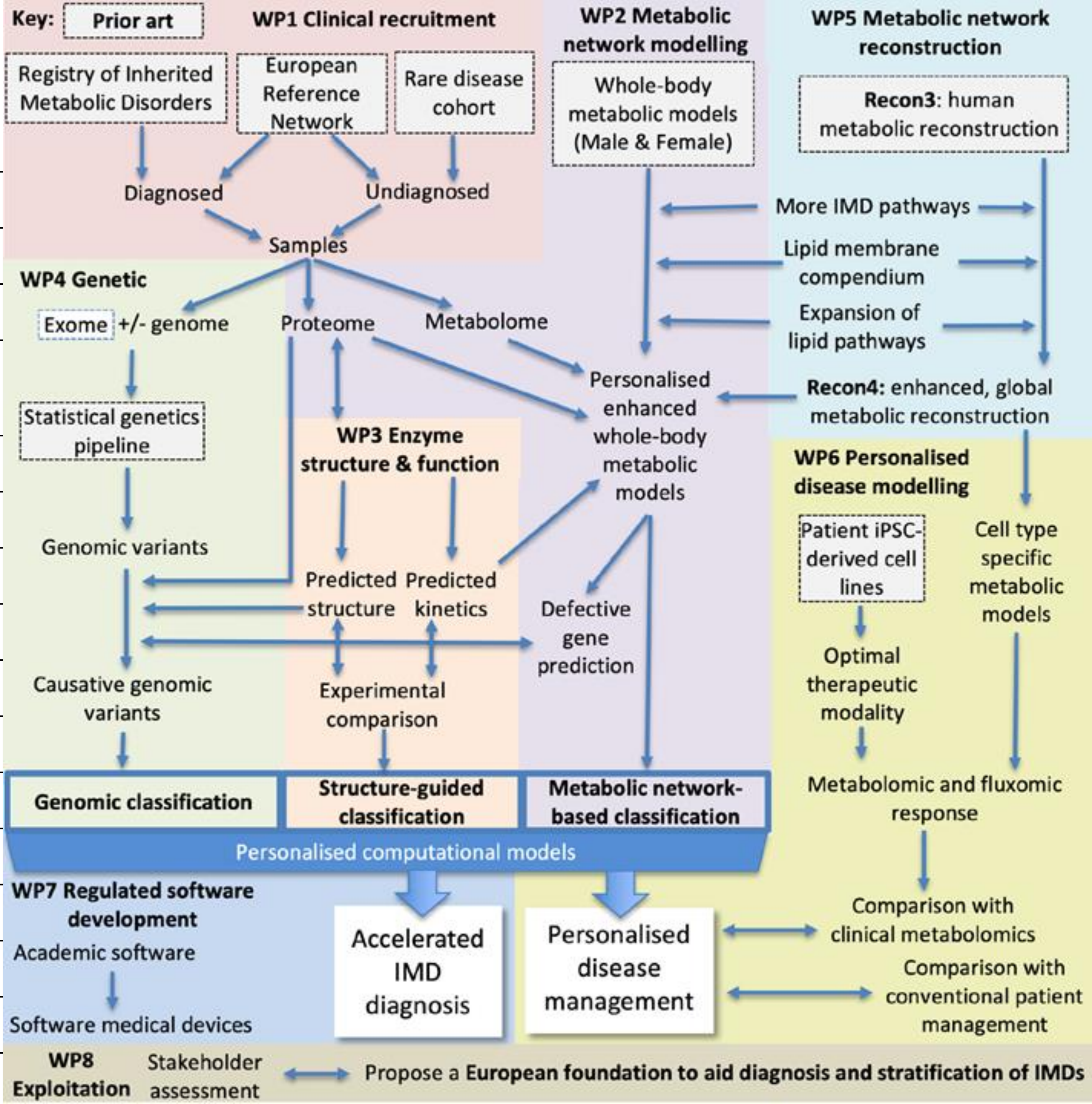


R.M.T.Fleming, N. Vlassis, I. Thiele, M.A. Saunders, Conditions for duality between fluxes and concentrations in biochemical networks, J. Theor. Biol., 409, 2016.

Reconstruction and Computational Modelling for Inherited Metabolic Diseases 2023-2028 www.recon4imd.org

Organisation	Co-PIs, ***also clinicians***
University of Galway	Ronan Fleming, Ines Thiele
Friuli Central University Hosp.	***Maurizio Scarpa***
Tuebingen University Hospital	Tobias Haack, Holm Graessner, *Olaf Riess*
University of Osnabrück	Joost Holthuis
Uni. Medical Centre Groningen	Barbara Bakker, ***Terry Derks***
Leiden University	T. Hankemeier, Hans Aerts
Dundalk IT	Fergal McCaffery
Newcastle University	Wyatt W. Yue
Swiss Institute of Bioinf.	Alan Bridge, Marco Pagni
University of Oxford	Brian Marsden
Heidelberg University Hospital	***Stefan Kölker***
UNIAMO FIMR Rome	Annalisa Scopinaro
Tech. University of Munich	Holger Prokisch
University College London	***Shamima Rahman***

+ 25 MetabERN HCPs = Clinical recruitment team



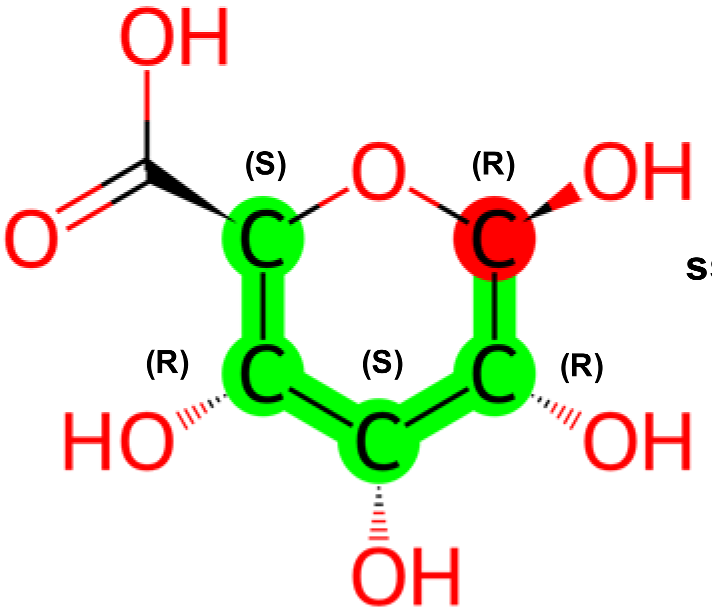
molDistance: A 2.5D Alignment Framework for Mapping Stereoisomers

- Cross-mapping metabolites problems due to stereoisomer variations.
- ReconX Knowledge Graph (ReconXKG*) integrates human metabolic network information from multiple resources**, but stereochemical mismatches persist.
- **molDistance** computes a stereo-sensitive similarity score **(ssc)**, using structural alignment and stereogenic feature comparison

Jack McGoldrick
Poster: C-069

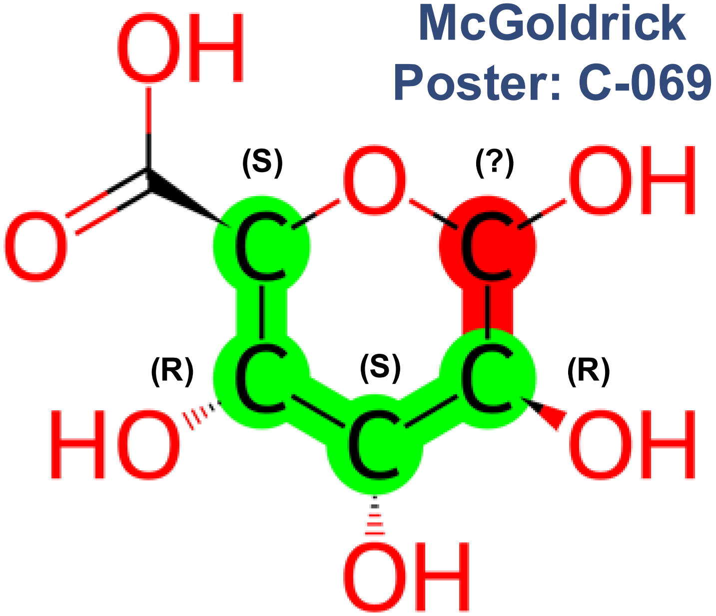
Example:

- Originally mapped as the same molecule (within ReconXKG)
- Now accurately remapped as *diastereomers* using molDistance



vmhM:pect (pectin)

ssc = 0.834



CHEBI:75525 (D-galactopyranuronate)

*Marco Pagni, Ines Thiele, Alan Bridge, et al., ReconX Knowledge Graph (under development)
** Virtual Metabolic Human, Rhea, SwissLipids, UniProt, MetaNetX, ChEBI, Literature, etc.

Cardinality Optimisation for Transparent and Fair Multi-Site Recruitment in Rare Disease Research: Application to Recon4IMD

Background

What Questions Does the Optimisation Problem Seek to Answer?

What IMDs? | How many Patients? | Which Hospitals? | Which Metabolomic lab?

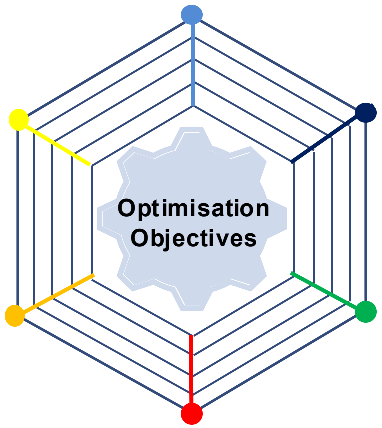
Farid Zare
Poster: C-115

Objectives

Maximum Number Of IMDs

Maximum Clinical Interest

Minimum Hospitals Per IMD



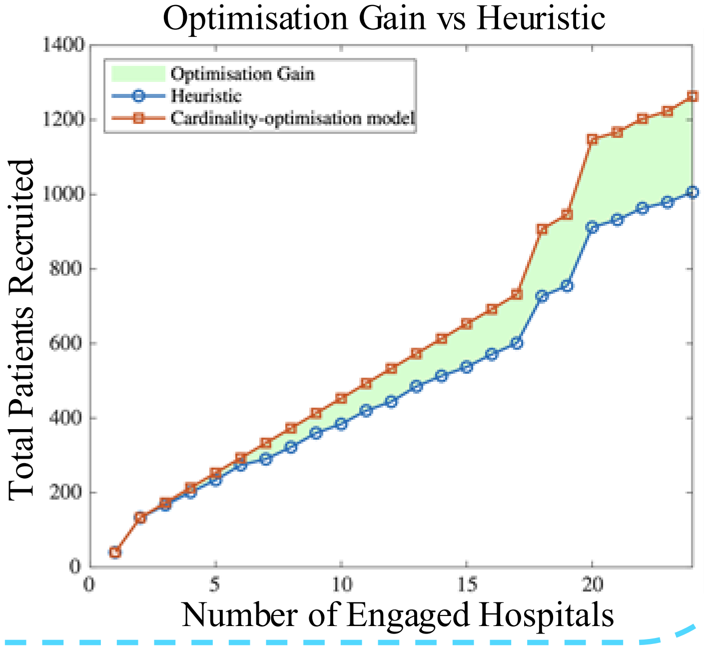
Minimum Metabolomic Cost

Minimum Metabolic Platform Per IMD

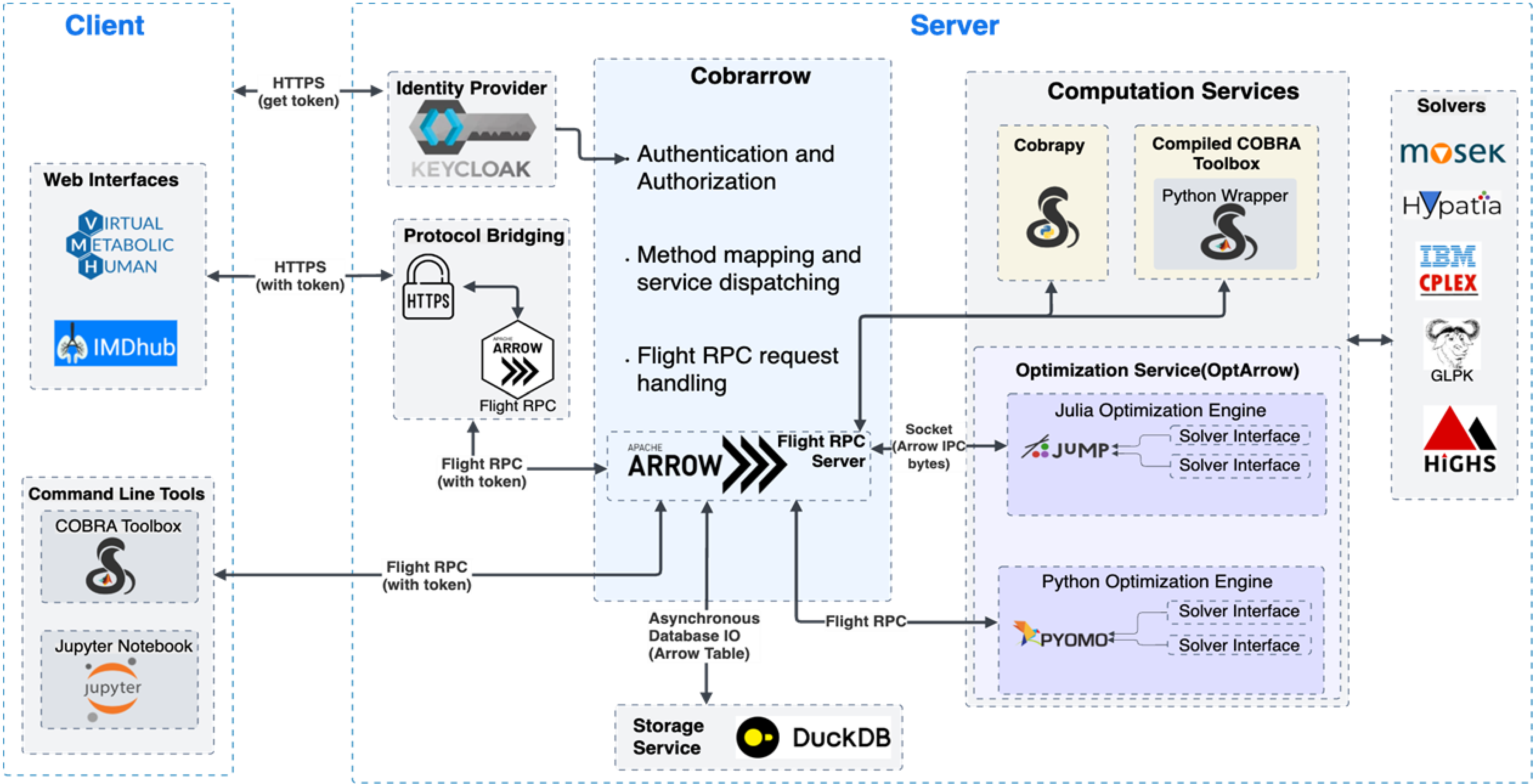
Minimum Shipment Cost

Results

Cardinality optimisation consistently yields higher recruitment in complex, multi-centre settings, where the heuristic model struggles with combinatorial complexity.



COBRArrow: interoperable high dimensional constraint-based modelling



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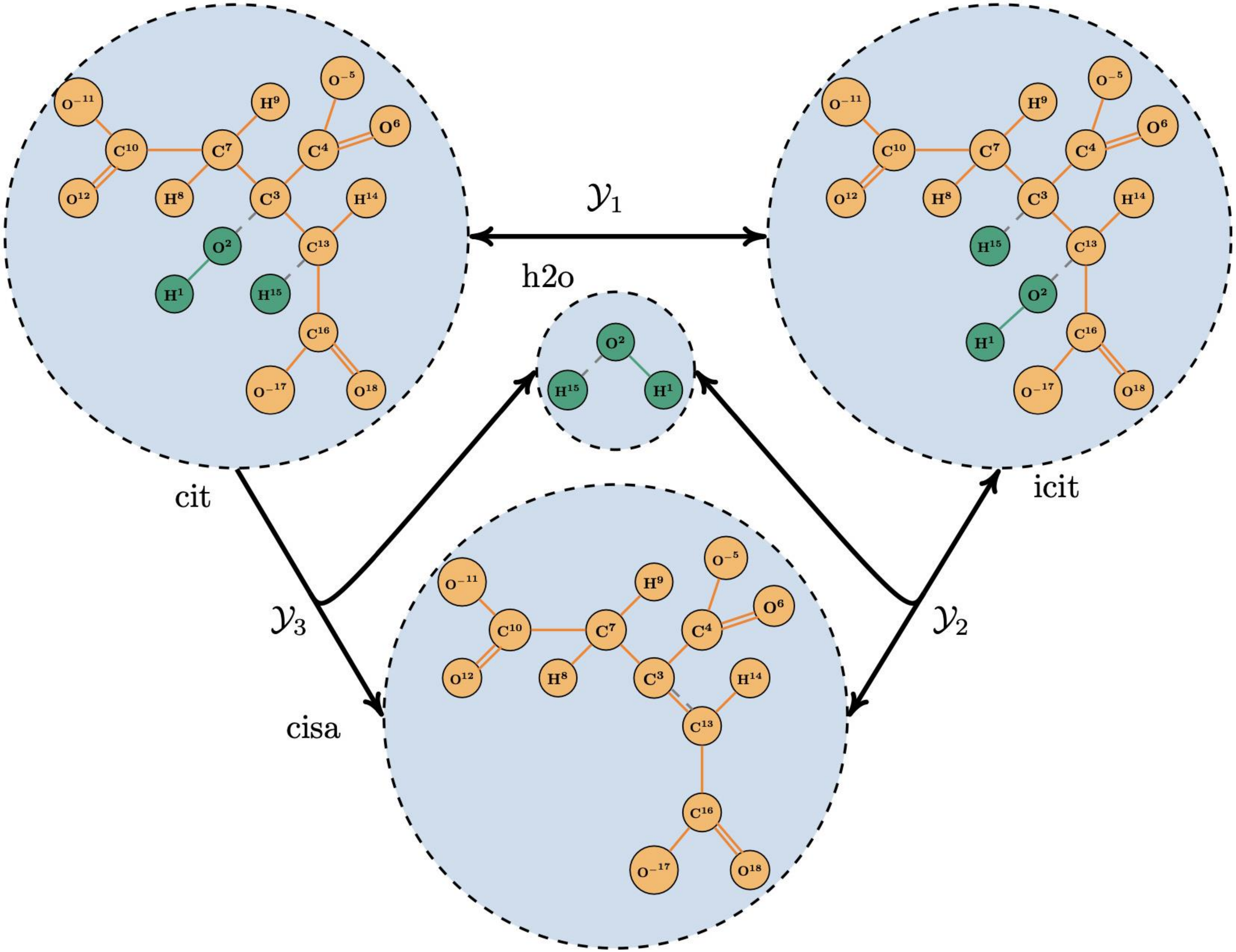
Michael Saunders, Stanford University,
Bernhard Palsson, UC San Diego,
Systems Biochemistry Group, Digital Metabolic Twin Center, Galway.

Acknowledgements: Recon4IMD consortium: www.recon4imd.org

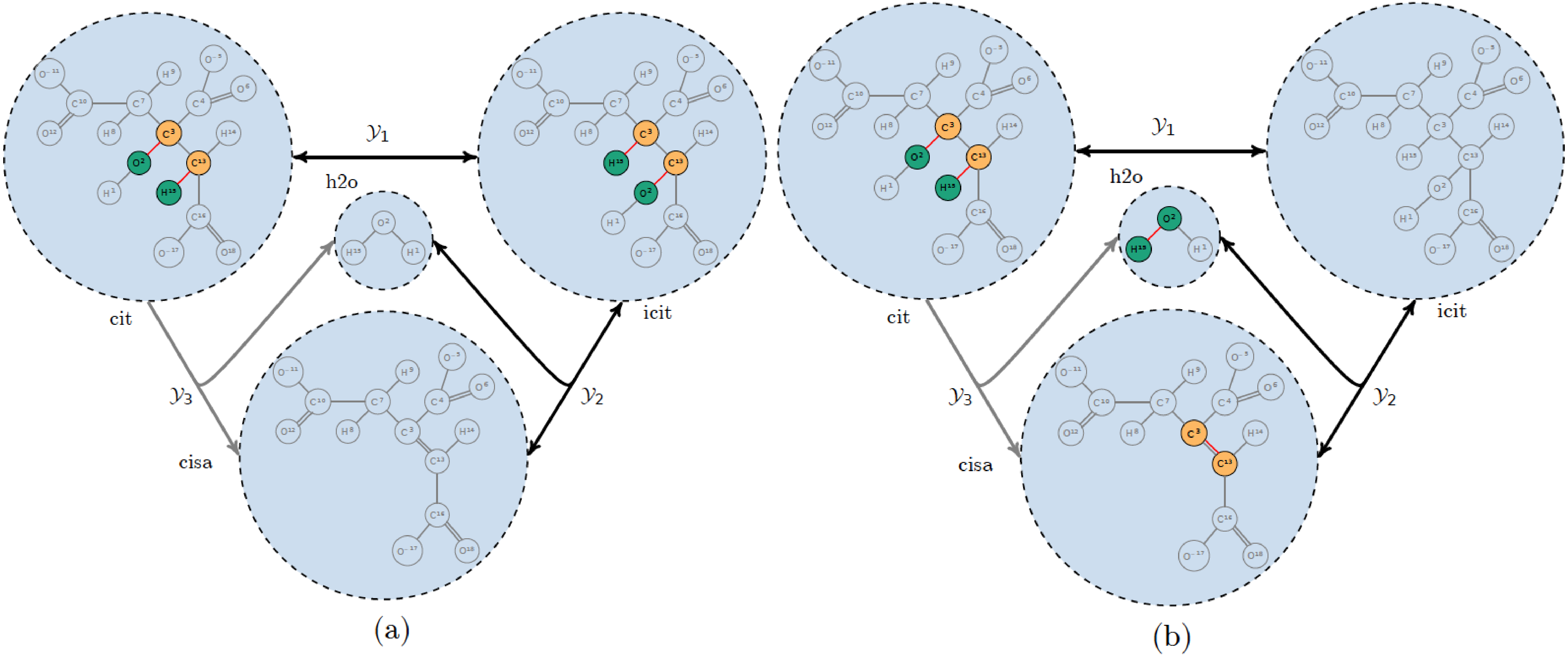
Recon4IMD is co-funded by the European Union's Horizon Europe Framework Programme (101080997), the Swiss State Secretariat for Education, Research and Innovation (23.00232), and by UK Research & Innovation (10083717 & 10080153).

Characterisation of conserved and reacting moieties in chemical reaction networks (submitted)

Hadjar Rahou, Hulda S. Haraldsdóttir, Filippo Martinelli, Ines Thiele, Ronan M. T. Fleming



Reacting moieties in chemical reaction networks



Characterisation of conserved and reacting moieties in chemical reaction networks (submitted)

Hadjar Rahou, Hulda S. Haraldsdóttir, Filippo Martinelli, Ines Thiele, Ronan M. T. Fleming

thermoKernel: a novel thermodynamically consistent model extraction algorithm

$$
\begin{aligned}
\min_{z,w,p,q,s,r} \quad & \beta 1^T(p+q) + g^T \|z\|_0 + h^T \|s\|_0 + f^T \|r\|_0 \\
\text{s.t.} \quad & Nz + Bw = 0, & \overline{z} \leq z \leq \underline{z}, \\
& z = p - q, & \overline{w} \leq w \leq \underline{w}, \\
& (F+R)(p+q) = s, & 0 \leq p, \\
& (F+R)z = r, & 0 \leq q.
\end{aligned}
$$

- $z \in \mathbb{R}^n$ is an internal reaction flux vector.
- $w \in \mathbb{R}^k$ is an external reaction flux vector.
- $p \in \mathbb{R}^n_{\geq 0}$ is forward net reaction flux.
- $q \in \mathbb{R}^n_{\geq 0}$ is reverse net reaction flux.
- $s \in \mathbb{R}^m_{\geq 0}$ is the sum of the rate of production and consumption of each metabolite.
- $r \in \mathbb{R}^m$ is an approximation to the sum of production and consumption of each metabolite due to net reaction flux.

Internal reaction directionality constraints only

$$\underline{z} \in \{0, -\infty\}^n \text{ and } \overline{z} \in \{0, \infty\}^n$$

Entropy maximisation with exponential cones

$$\min_{v_f, v_r, c} \quad c_{e_f}^T \cdot e_f + c_{e_r}^T \cdot e_r + c_{e_c}^T \cdot e_c$$

$$\begin{pmatrix} 1^T(v_f + v_r) \\ v_f \\ -e_f \end{pmatrix} \in \mathcal{K}_{exp}^n \quad \Longleftrightarrow \quad -e_f \geq v_f \circ \log\left(\frac{v_f}{1^T(v_f + v_r)}\right)$$

$$\begin{pmatrix} 1^T(v_f + v_r) \\ v_r \\ -e_r \end{pmatrix} \in \mathcal{K}_{exp}^n \quad \Longleftrightarrow \quad -e_r \geq v_r \circ \log\left(\frac{v_r}{1^T(v_f + v_r)}\right)$$

$$\begin{pmatrix} 1 \\ c \\ -e_c \end{pmatrix} \in \mathcal{K}_{exp}^m \quad \Longleftrightarrow \quad -e_c \geq c \circ \log\left(\frac{c}{1^T c}\right)$$