Data Challenges in Systems Modelling

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The Mathematical Modelling Process

STEP 1

Identify the problem.

Detail the attributes of the system (variables and parameters).
Consider available data (if any).

STEP 2

Decide on modelling approach
(discrete vs. continuous,
temporal and/or spatial)

Write down a model.

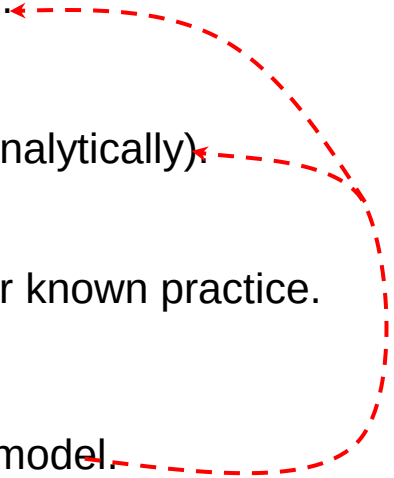
STEP 3

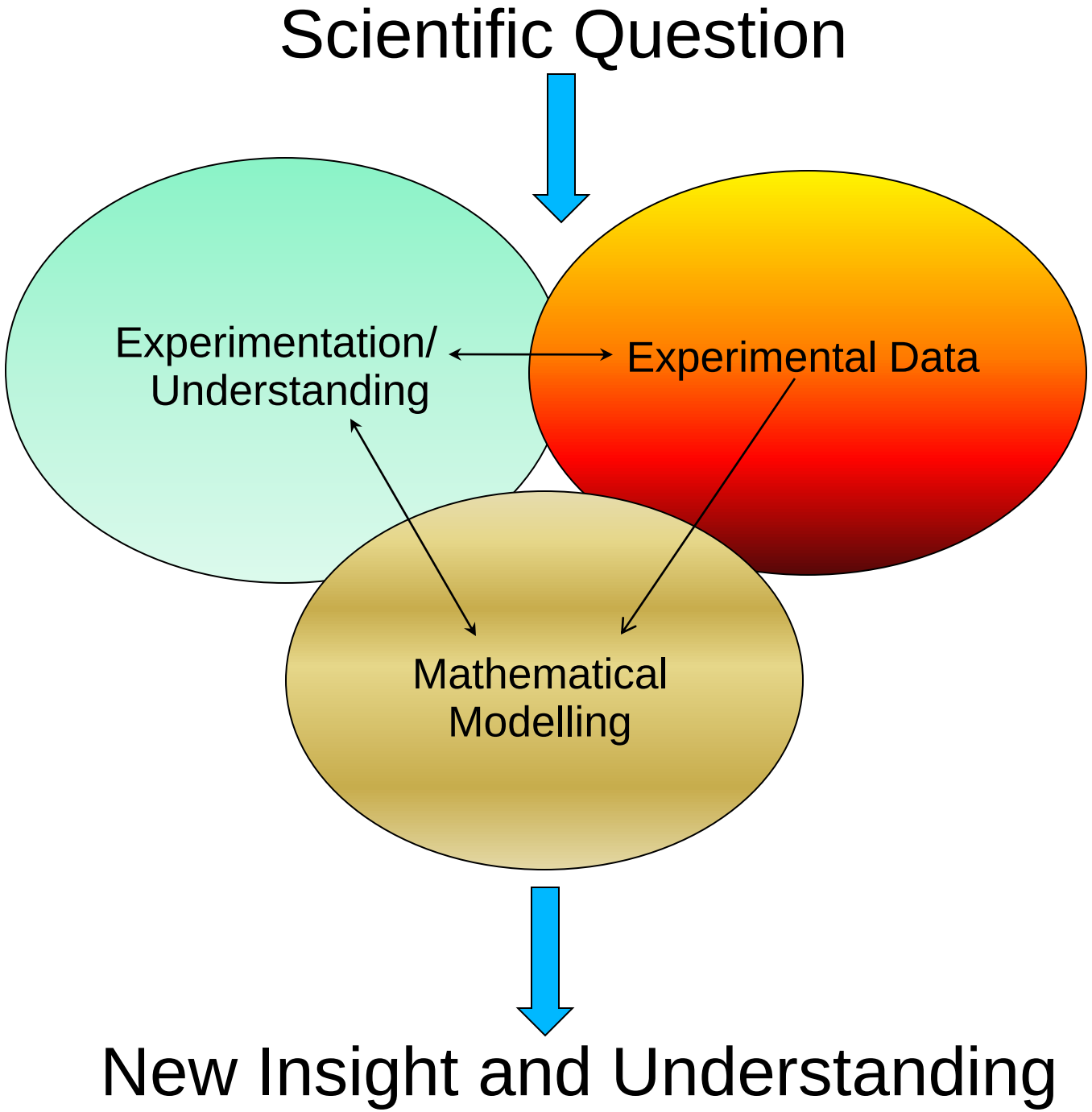
Solve it (computationally or analytically).

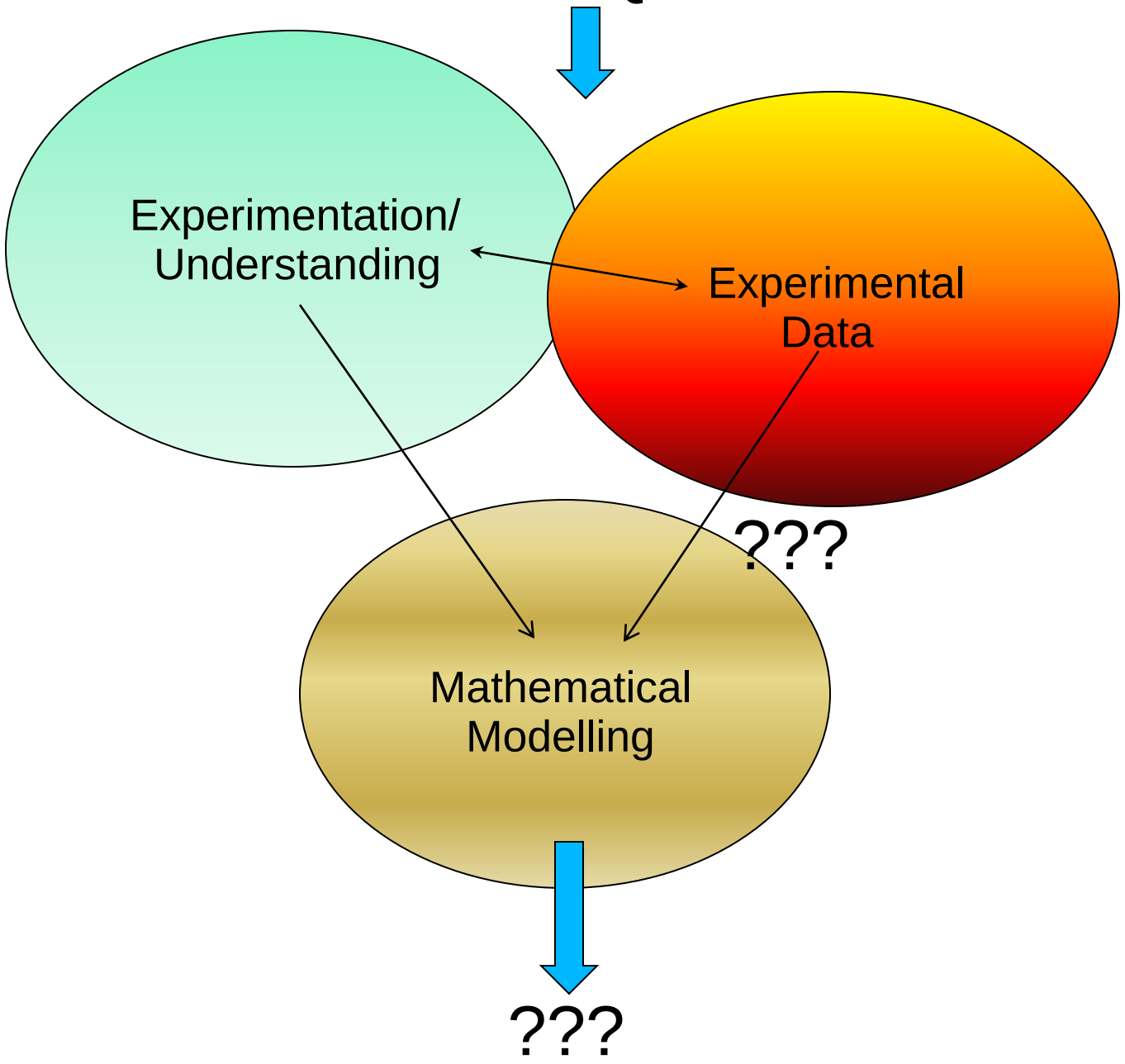
Test model outcomes with data or known practice.

STEP 4

Revise and improve the model.

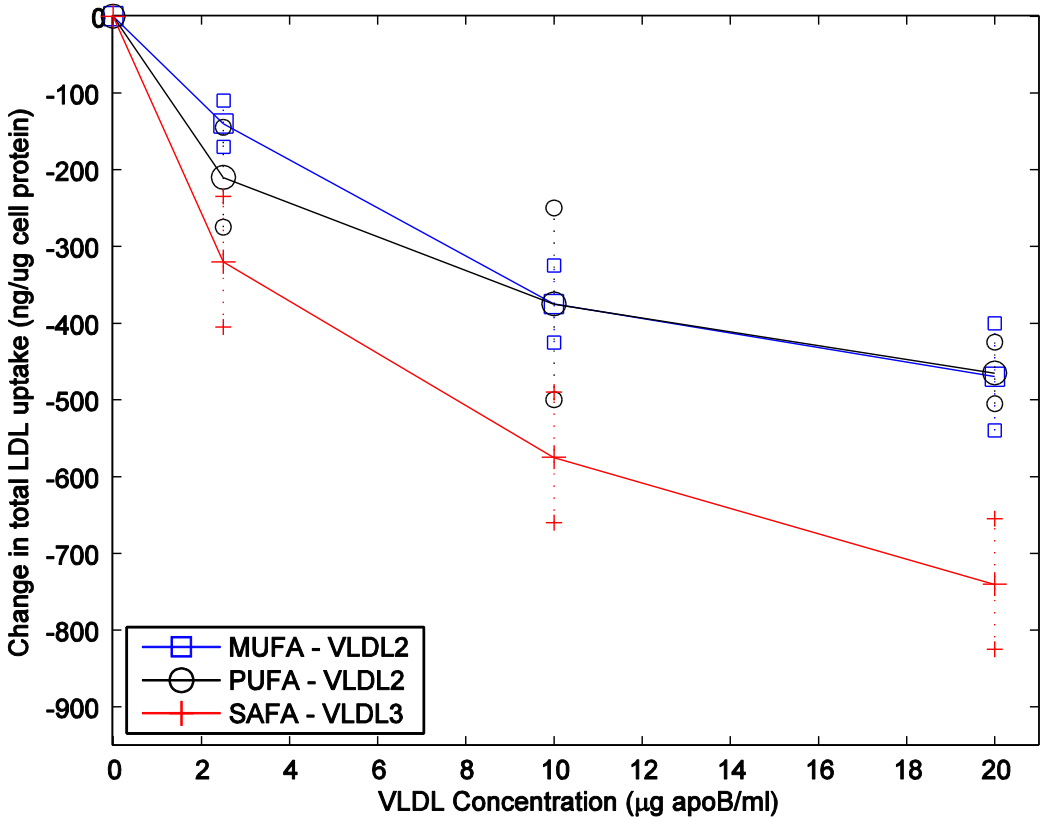



Scientific Question
Experimentation/
Understanding
Experimental Data
Mathematical
Modelling
New Insight and Understanding


Scientific Question
Experimentation/
Understanding
Experimental
Data
???
Mathematical
Modelling
???

Lipoprotein Metabolism

- Consider the uptake of LDL and VLDL particles by a single hepatocyte cell.



Jackson, K., Maitin, V., Leake, D., Yaqoob, P. and Williams, C. (2006). Saturated fat induced changes In S_f 60-400 particle composition reduces uptake of LDL by HepG2. *J. Lipid Res.*, 47:393-403.

Hypothesis Testing

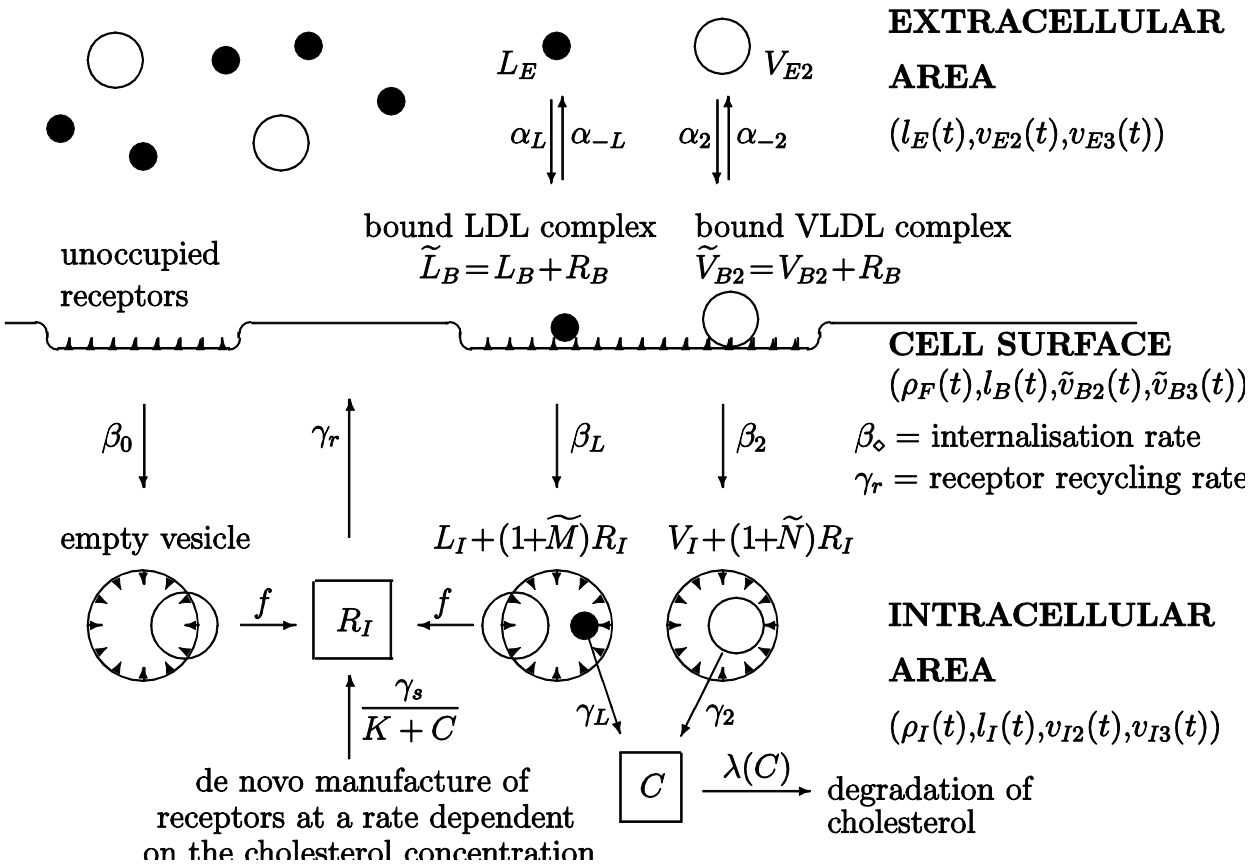
- Two hypothesis regarding LDL uptake

  Hypothesis 1 – VLDL particles reduce LDL uptake by blocking access to hepatocyte surface receptors. Particles either bind to the surface and are not internalised or are simply present in the pit.

  Hypothesis 2 – VLDL particles enter the pit, bind to receptors via apoE and are internalised by the cell.

  Which of these is correct?

The Model



- LDL (extracellular, bound and intracellular).
- VLDL-2 (extracellular, bound and intracellular).
-VLDL-3 (extracellular, bound and intracellular).
- Free, bound and internalised receptors.
- Cholesterol concentration.

The Model

$$L_E + R_F + (M-1)R_F \underset{\alpha_{-L}}{\overset{\alpha_L}{\Leftrightarrow}} L_B \cdot MR_B$$

LDL binding

$$L_B \cdot MR_B + \tilde{M}R_F \rightarrow L_I + (M+\tilde{M})R_I$$

LDL and receptor internalisation

$$L_I \xrightarrow{\gamma_L} R_L^{chol} C$$

LDL to cholesterol release

$$PR_F \xrightarrow{\beta_0} PR_I$$

Free receptor internalisation

The Model

$$W\frac{dl_E}{dt} = -\alpha_L \rho_F l_E + \alpha_{-L} l_B$$

$$\frac{dl_B}{dt} = \alpha_L \rho_F l_E - \alpha_{-L} l_B - \beta_L l_B$$

$$\frac{dl_I}{dt} = \beta_L l_B - \gamma_L l_I$$

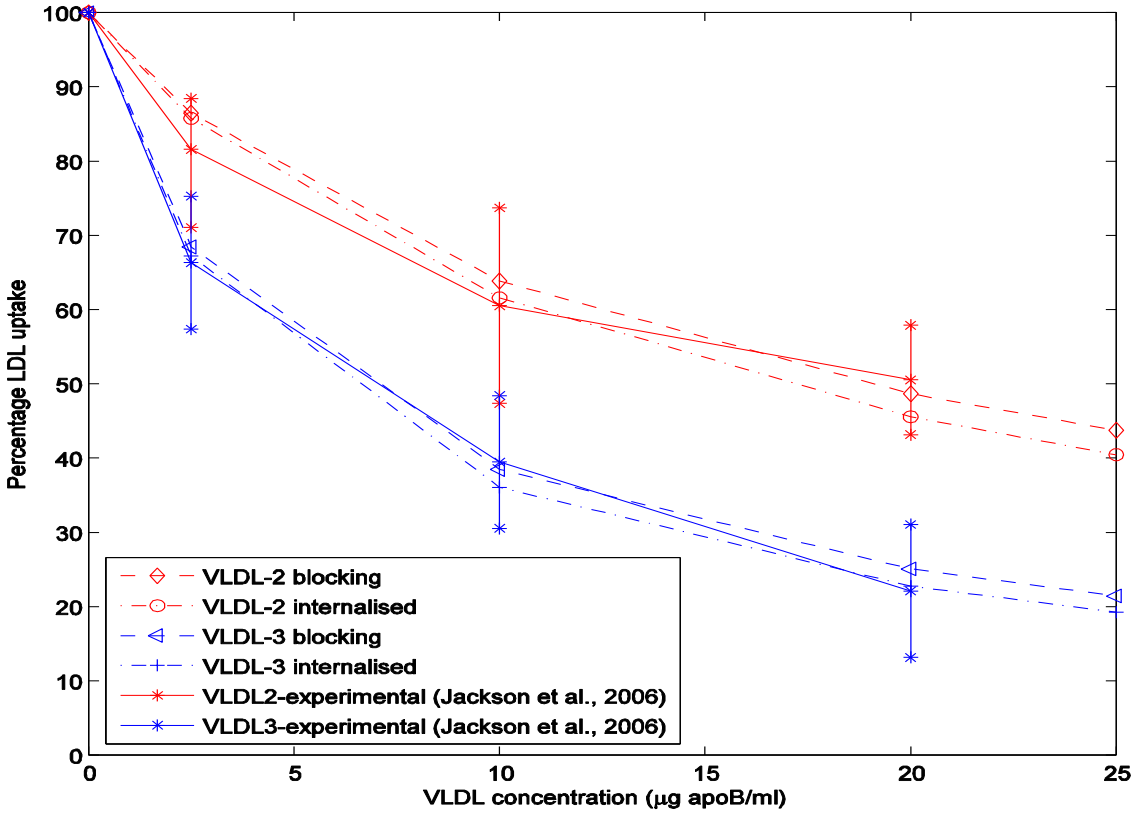
with

$$l_E(0) = l_0, \quad l_B(0) = 0, \quad l_I(0) = 0.$$

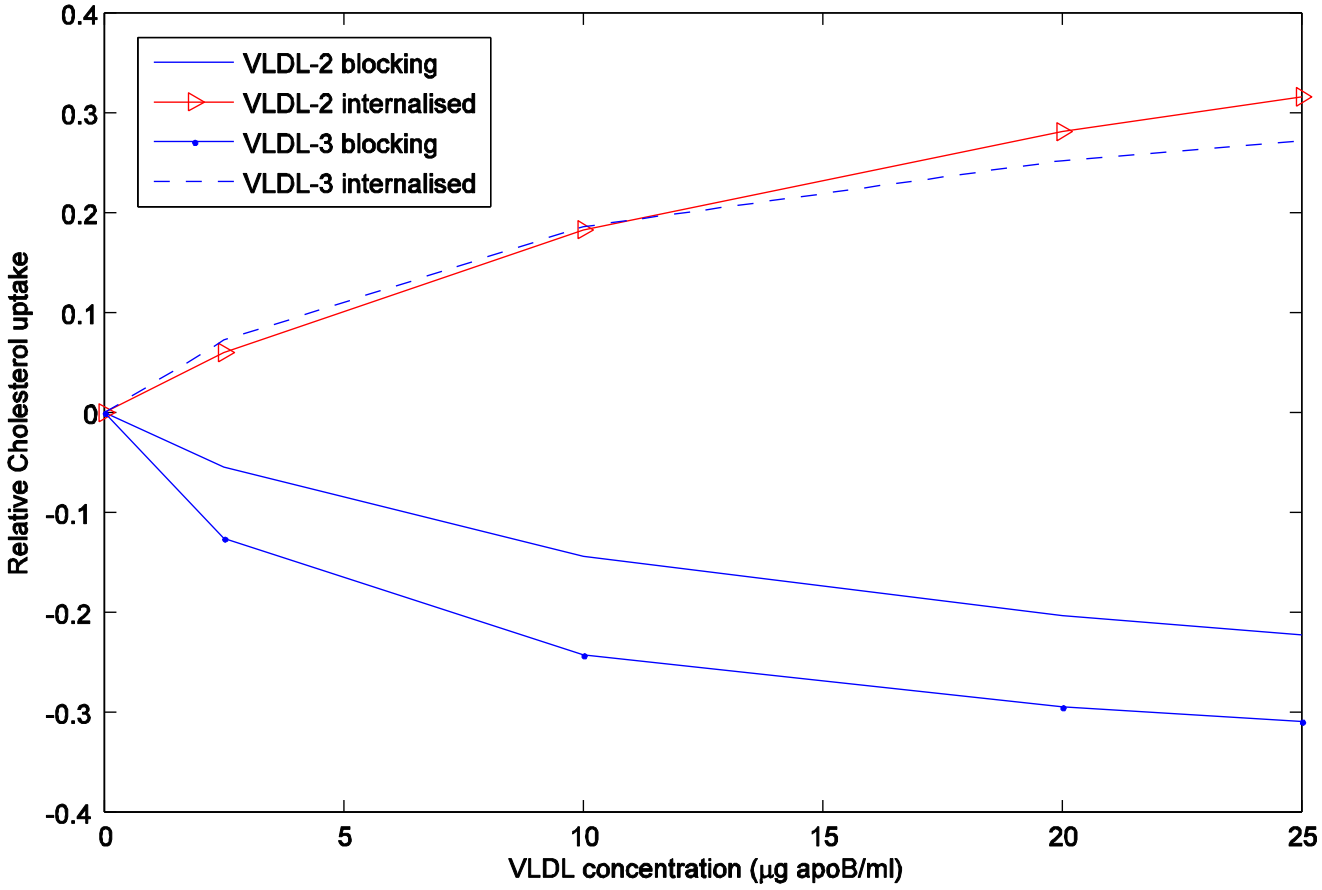
Experimental Data

Parameter	Description	Value
P	Number of pits per cell.	180
	Number of receptors per cell.	35,000
	Number of receptors per pit (only 70% in pits).	180
	Radius of an LDL particle.	10 nm
	Radius of a VLDL particle.	15–40 nm
	Typical radius of a pit.	100 nm
M	Number of receptors covered by a bound LDL.	1
N	Number of receptors covered by a bound VLDL-2.	2
Q	Number of receptors covered by a bound VLDL-3.	3.6
$\overline{M}, \overline{N}, \overline{Q}$	Maximum number of additional free receptors internalised.	M, N, Q
α_L	Rate of LDL binding to free receptors.	6.66×10^{-17} ml/molecules s
α_2, α_3	Rate of VLDL-2, VLDL-3 binding to free receptors.	$14.0\alpha_L$, $24\alpha_L$
β_L	Rate of LDL internalisation.	$2.7 \times 10^{-3}\,s^{-1}$
β_2, β_3	Rate of VLDL-2 and VLDL-3 internalisation.	β_L
β_0	Rate of unbound receptor internalisation.	0
α_{-L}	Rate of LDL unbinding from receptors.	$5.9 \times 10^{-4}\,s^{-1}$
α_{-2}, α_{-3}	Rate of VLDL-2, VLDL-3 unbinding from receptors.	$0.5\alpha_{-L}$, $0.33\alpha_{-L}$
γ_L	Rate of conversion of internalised LDL to cholesterol.	~1/300 s
γ_2, γ_3	Rate of receptor recycling from bound VLDL.	γ_L
γ_r	Rate of receptor recycling.	$0.01\,s^{-1}$
f	Fraction of receptors recycled.	0.9
K	Constant for receptor production.	$2C_e$
γ_s	Rate of free receptor production by cell.	1.8×10^{30} molecules/ml s
λ	Rate of breakdown of cholesterol.	$3.3 \times 10^{-3}\,s^{-1}$
g_L^{chol}	Average cholesterol content per LDL particle.	3400
g_{V-2}^{chol}	Average cholesterol content per VLDL-2 particle.	3100
g_{V-3}^{chol}	Average cholesterol content per VLDL-3 particle.	3900
ρ_0	Initial concentration of free receptors.	2.5×10^6/cell
C_e	Maximum cholesterol content of a hepatocyte.	2.65×10^{19} molecules/ml
ρ_0	Initial concentration of free receptors.	2.17×10^{10} receptors/ml
l_0	Initial concentration of LDL particles (mass/vol).	10 μg/ml
l_0	Initial concentration of LDL particles (no./vol).	1.17×10^{13} particles/ml
v_{02}/v_{03}	Typical concentration of VLDL particles (mass/vol).	2.5, 10 and 20 μg/ml
v_{02}/v_{03}	Initial concentration of VLDL particles (no./vol).	2.95×10^{12}, 1.17×10^{13} and 2.35×10^{13} particles/ml medium
W	Volume ratio of cell culture medium to cell volume.	1.50×10^3
h_2, h_3	Hypothesis: if $h = 2$, VLDL is internalised. if $h = 1$, VLDL blocks and is not internalised.	1,2

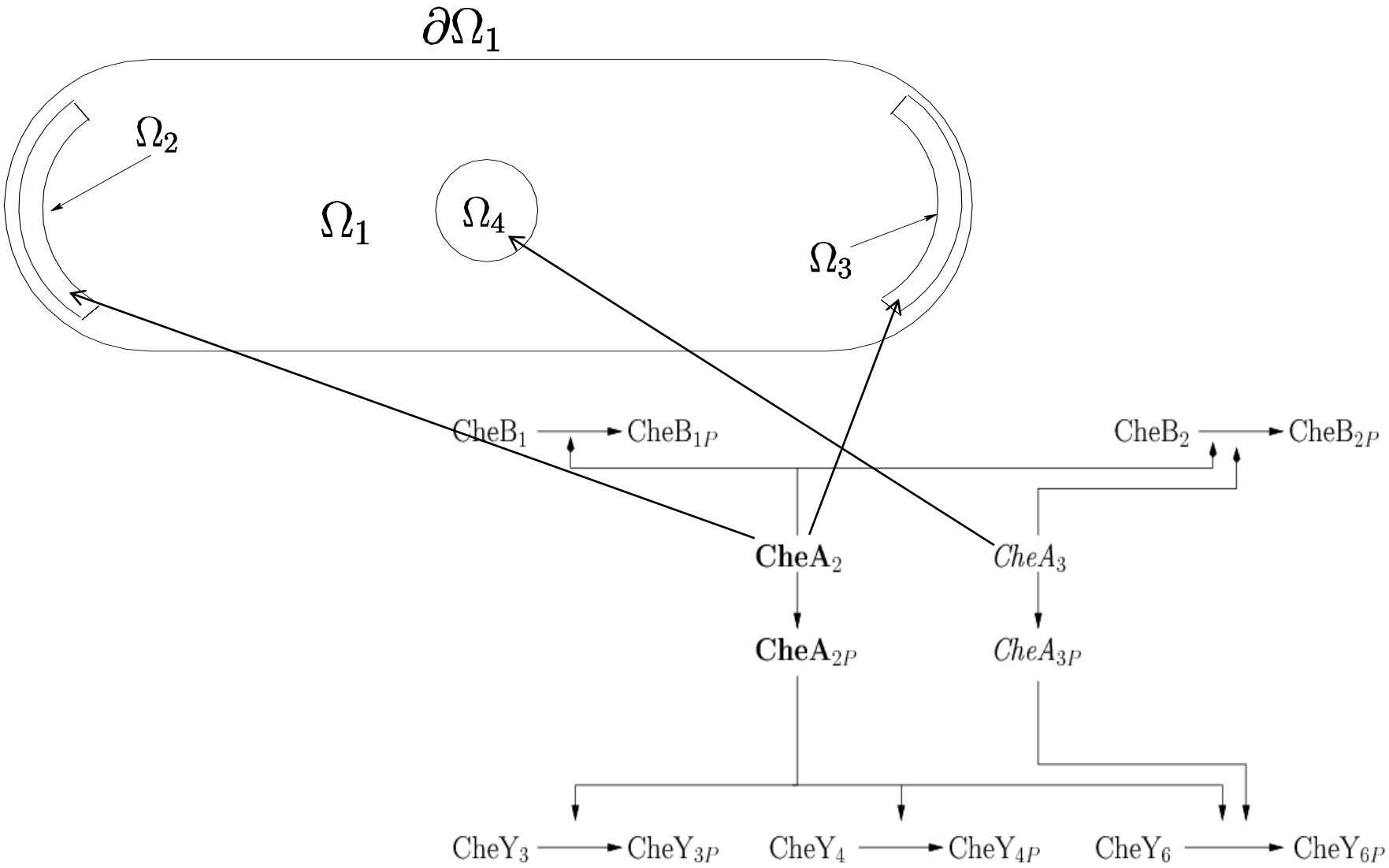
Model and Experimental Comparisons



New Insight


VLDL-2 blocking
VLDL-2 internalised
VLDL-3 blocking
VLDL-3 internalised
Relative Cholesterol uptake
VLDL concentration (µg apoB/ml)
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
0
5
10
15
20
25

Rhodobacter sphaeroides



Rhodobacter sphaeroides – Phosphotransfer pathways

$A_2 \longrightarrow A_{2P}$

$A_{2P} + Y_3 \longleftrightarrow A_2 + Y_{3P}$

$A_{2P} + Y_4 \longleftrightarrow A_2 + Y_{4P}$

$A_{2P} + Y_6 \longleftrightarrow A_2 + Y_{6P}$

$A_{2P} + B_1 \longleftrightarrow A_2 + B_{1P}$

$A_{2P} + B_2 \longleftrightarrow A_2 + B_{2P}$

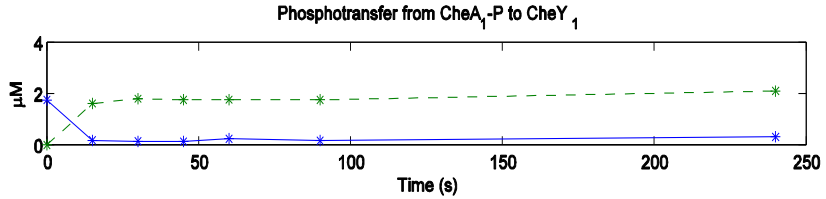
Are the cytoplasmic and polar receptor clusters connected?

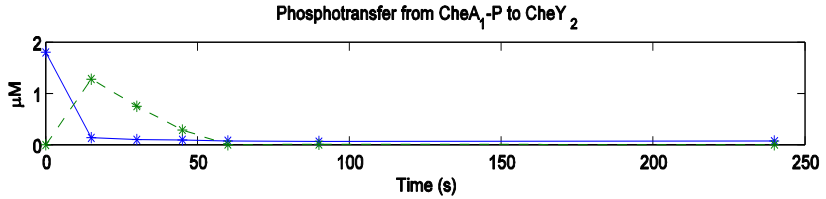
$A_3 \longrightarrow A_{3P}$

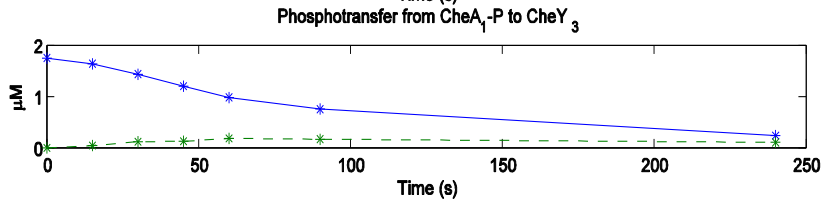
$A_{3P} + Y_6 \longleftrightarrow A_3 + Y_{6P}$

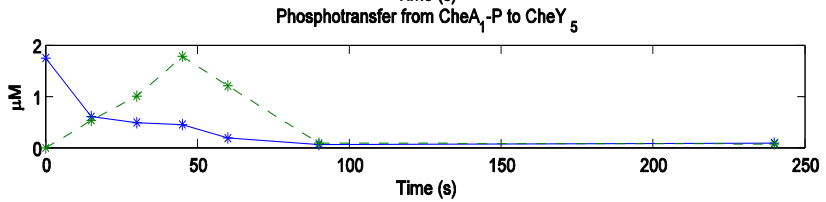
$A_{2P} + B_2 \longleftrightarrow A_2 + B_{2P}$

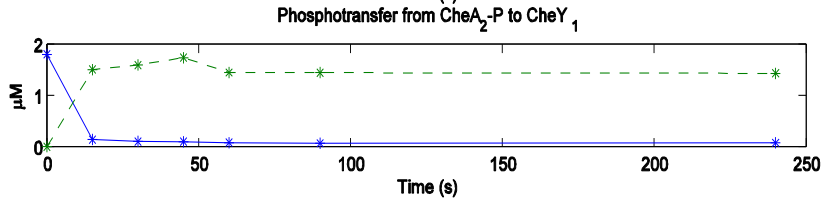
R. sphaeroides – Experimental Data

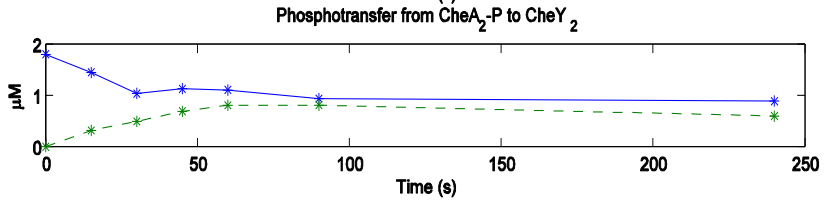


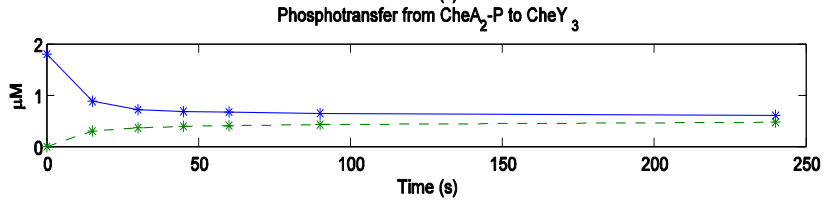


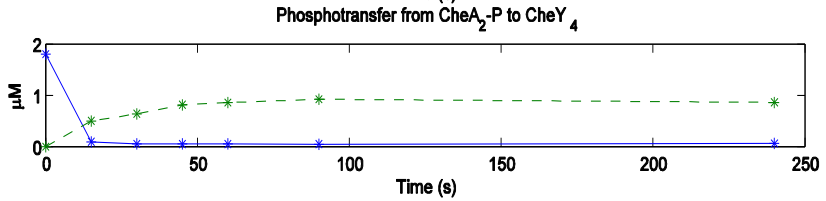


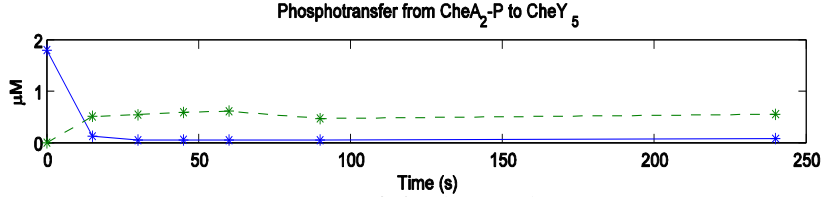


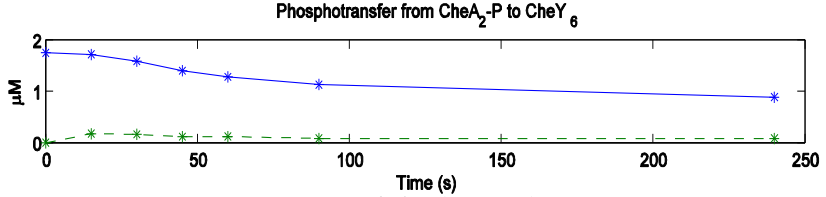


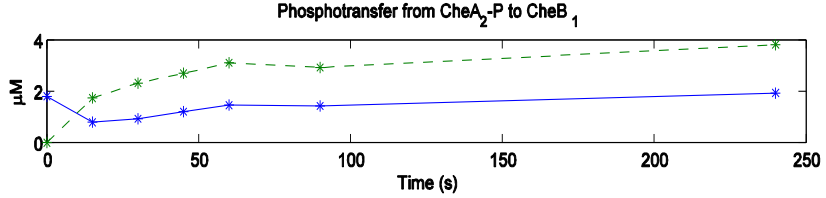


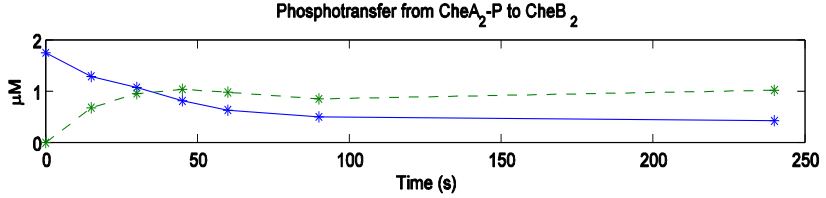












R. sphaeroides – Model parameterisation

$$\begin{aligned}
\mathrm{CheA}_i + \mathrm{ATP} &\underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{CheA}_i \cdot \mathrm{ATP} \xrightarrow{k_1} \mathrm{CheA}_{iP} + \mathrm{ADP} \\
\mathrm{CheA}_{iP} + \mathrm{CheY}_j &\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{CheA}_i + \mathrm{CheY}_{jP} \\
\mathrm{CheY}_{jP} + \mathrm{H_2O} &\xrightarrow{k_3} \mathrm{CheY}_j + \mathrm{Phosphate}
\end{aligned}$$

Applying the law-of-mass action

$$\begin{aligned}
\frac{\mathrm{d}A_P}{\mathrm{d}t} &= k_1 C - k_2 A_P (Y_T - Y_P) + k_{-2}(A_T - A_P - C) Y_P \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= -k_+ (A_T - A_P - C) S + k_- C \\
\frac{\mathrm{d}C}{\mathrm{d}t} &= k_+ (A_T - A_P - C) S - (k_- + k_1) C \\
\frac{\mathrm{d}Y_P}{\mathrm{d}t} &= k_2 A_P (Y_T - Y_P) - k_{-2}(A_T - A_P - C) Y_P - k_3 Y_P
\end{aligned}$$

with the initial conditions

$$A_P = A_{P0}, \qquad S = S_0, \qquad C = C_0 \qquad \text{and} \quad Y = Y_0$$

R. sphaeroides – Model parameterisation

Model Reduction I

$$
\begin{aligned}
\frac{\mathrm{d}A_P}{\mathrm{d}t} &= \frac{k_1(A_T - A_P)S}{S+K} - k_2 A_P(Y_T - Y_P) + k_{-2}\left(A_T - A_P - \frac{k_1(A_T - A_P)S}{S+K}\right)Y_P, \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= -k_+\left(A_T - A_P - \frac{(A_T - A_P)S}{S+K}\right) + \frac{k_-(A_T - A_P)S}{S+K}, \\
\frac{\mathrm{d}Y_P}{\mathrm{d}t} &= k_2 A_P(Y_T - Y_P) - k_{-2}\left(A_T - A_P - \frac{(A_T - A_P)S}{S+K}\right)Y_P - k_3 Y_P,
\end{aligned}
$$

with the initial conditions

$$A_P = A_{P0}, \qquad S = S_0 \quad \text{and} \quad Y_P = Y_{P0}.$$

and

$$C = \frac{(A_T - A_P)S}{S+K},$$

where $K = (k_- + k_1)/k_+$

R. sphaeroides – Model parameterisation

Model Reduction II

$$\begin{aligned}
\frac{\mathrm{d}A_P}{\mathrm{d}t} &= k_1 M(A_T - A_P) - k_2 A_P(Y_T - Y_P) + k_{-2}(A_T - A_P)(1 - M)Y_P, \\
\frac{\mathrm{d}Y_P}{\mathrm{d}t} &= k_2 A_P(Y_T - Y_P) - k_{-2}(A_T - A_P)(1 - M)Y_P - k_3 Y_P,
\end{aligned}$$

where $M = S/(S + K)$ is a constant with

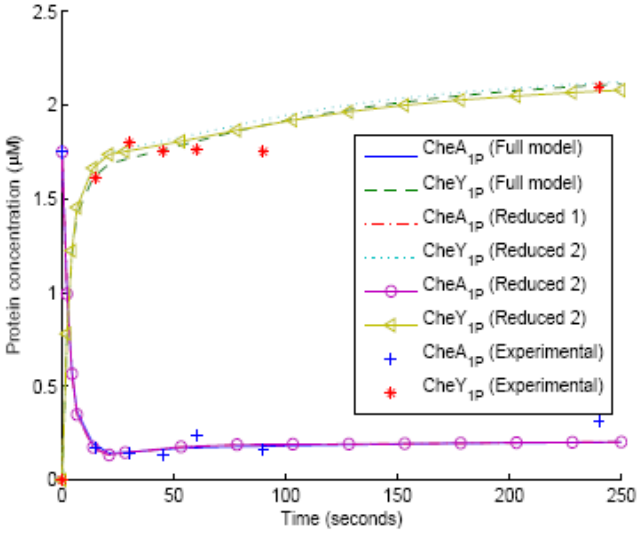
$$A_P = A_{P0} \quad \text{and} \quad Y_P = Y_{P0}, \quad \text{at} \quad t = 0.$$

R. sphaeroides – Model parameterisation

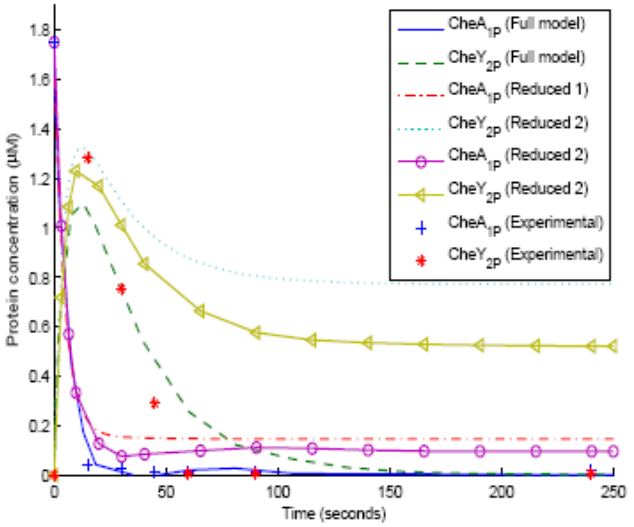
Numerical optimisation (parameter fitting)

- Apply and compare a range of numerical optimisation methods for obtaining model parameters from experimental data.

- Allows us to compare various fits to the data to obtain the most robust set of parameters (as well as the method fits).



(a) CheA_{1P} to CheY_1.

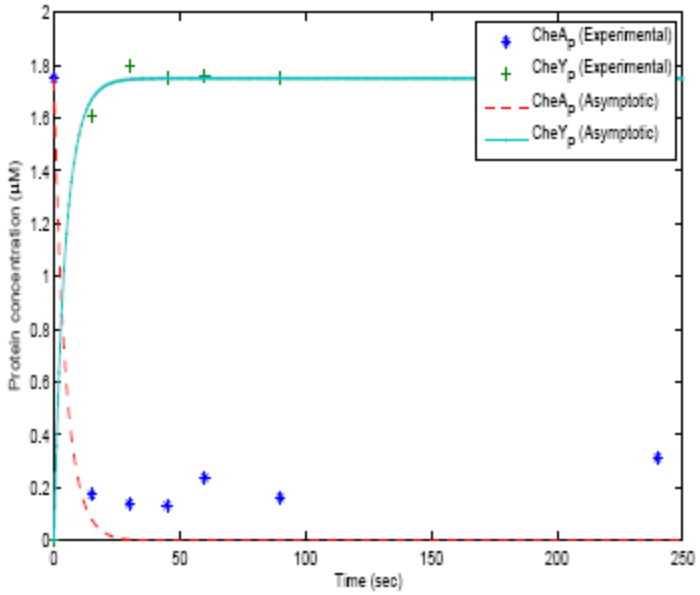


(b) CheA_{1P} to CheY_2.

R. sphaeroides – Model parameterisation

Asymptotic approximations to Reduced Model II

- Consider various limits.
- Rapid phosphotransfer ($\bar{k}_2 \sim O(1/\varepsilon)$)



(a) CheA_{1P} to CheY_1.

- Inner *O(1)* asymptotic expansion for CheA_P

$$X_0(t) = \frac{(K - x_{P0})}{\left(\left(\frac{K - x_{P0}}{x_{P0}} + 1\right) e^{k_2 x_T (K - x_{P0})t} - 1\right)}$$

R. sphaeroides – Model parameterisation

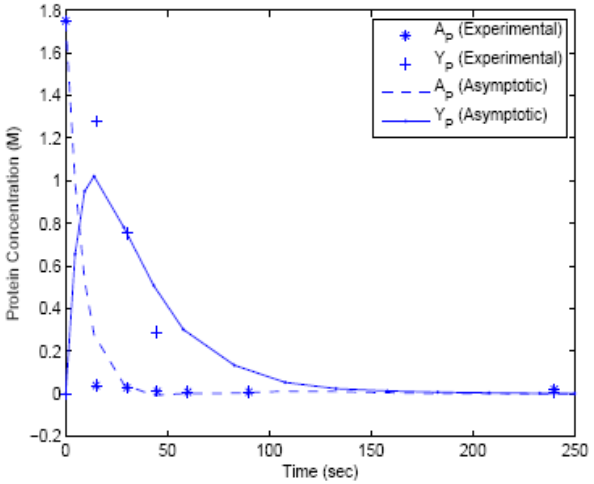
- Rapid phosphotransfer and dephosphorylation ($\bar{k}_2, \bar{k}_3 \sim O(1/\varepsilon)$)
- Inner *O(1)* asymptotic expansion for $\mathrm{CheA_P}$ and $\mathrm{CheY_P}$

$$\frac{\mathrm{d}X_0}{\mathrm{d}T} = -X_0(K - Y_0)$$
$$\frac{\mathrm{d}Y_0}{\mathrm{d}T} = X_0(K - Y_0) - \alpha Y_0$$

with

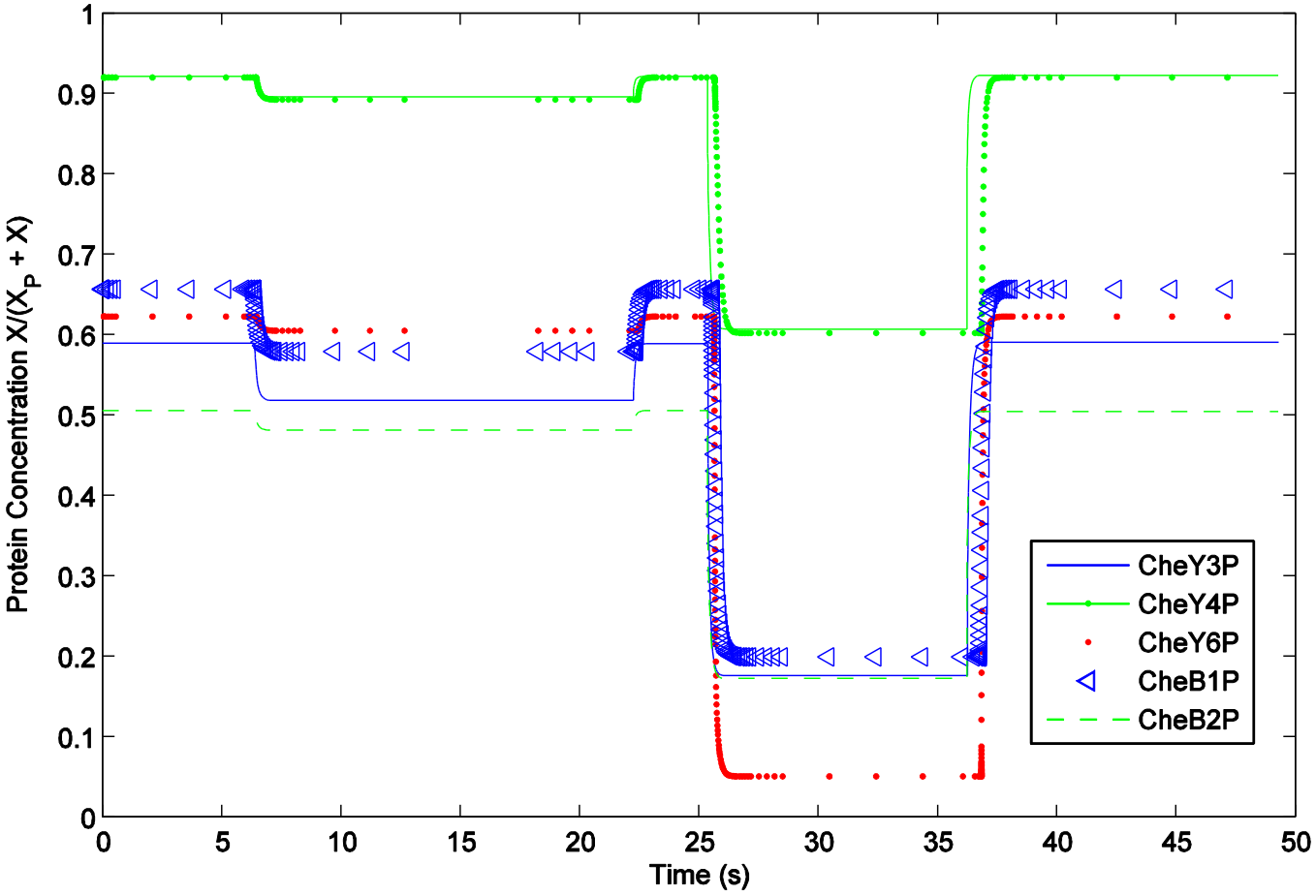
$X_0(0)=X_{P0}$ and $Y_0(0)=Y_{P0}$,

where $\alpha=k_3/k_2$.

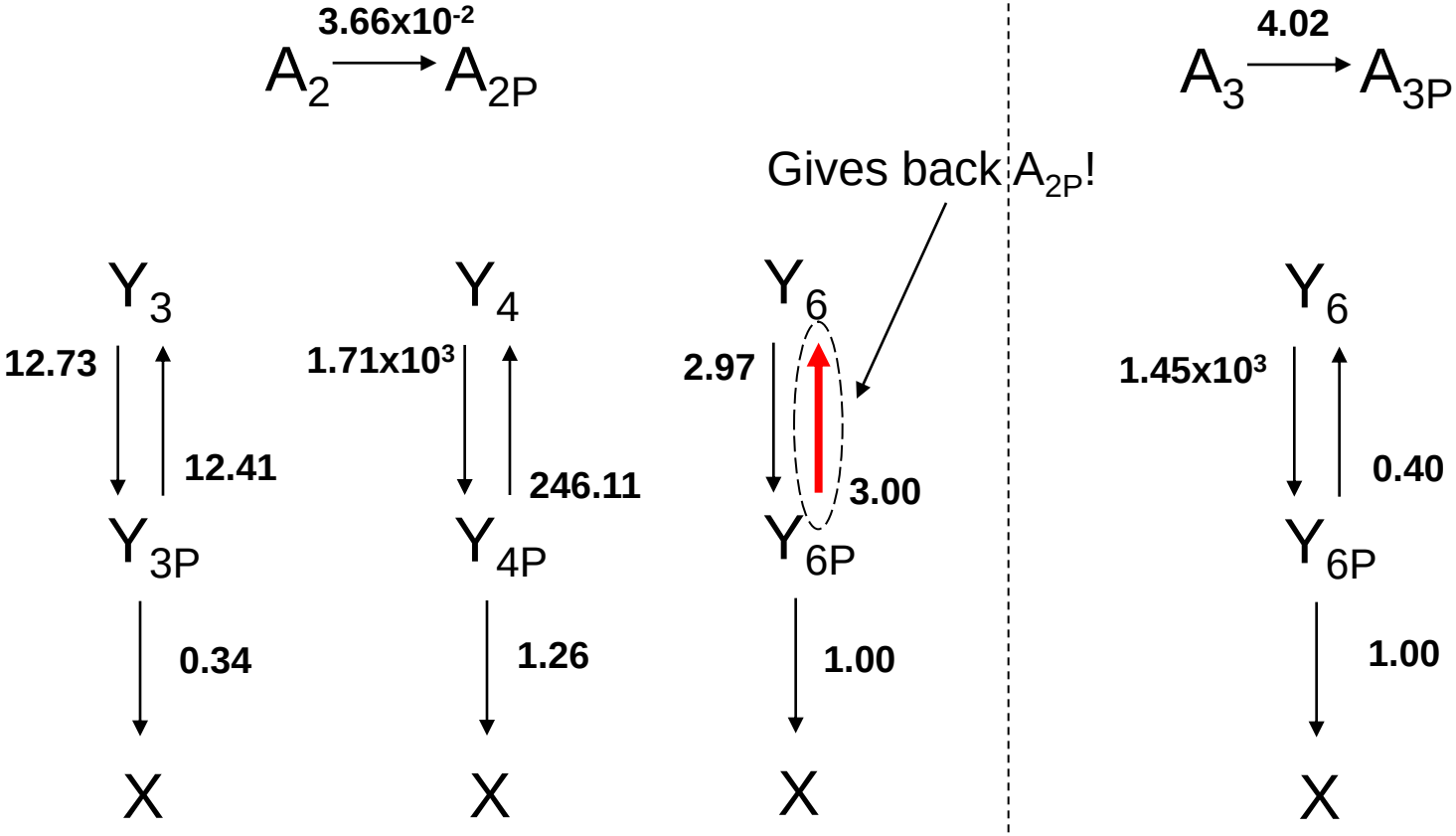


(b) CheA_{1P} to CheY_2.

R. sphaeroides - The importance of the cytoplasmic cluster



R. sphaeroides - Phosphorelay pathway



R. sphaeroides - Experimental Results

Time (s)	A3-P	B2-P	A2-P
0	21.21	0	0
15	20.58	0.97	0.03
30	21.55	0.92	0.03
60	20.55	0.92	0.05
120	19.70	0.94	0.07
240	19.29	1.00	0.11

Acknowledgements

Bacterial chemotaxis

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Lipoprotein metabolism

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- Dr Kim Jackson, Food Biosciences, University of Reading.
- Prof. Christine Williams, Food Biosciences, University of Reading.
- Unilever Corporate Research.

Publications

Tindall, M.J., Determining model parameters from experimental data: Model reduction, numerical optimisation and asymptotic methods. In preparation.

Tindall, M.J., Porter, S.L., Maini, P.K. and Armitage, J.P. Identification of a phosphorelay in Rhodobacter sphaeroides predicted by mathematical modelling. In preparation.

Tindall MJ, Wattis JA, O'Malley BJ, Pickersgill L, Jackson KG. A continuum receptor model of hepatic lipoprotein metabolism. *J. Theor. Biol.* 2009 Apr 7;257(3):371-84, 2009.

Tindall, M.J., Porter, S.L., Wadhams, G., Maini, P.K. and Armitage, J.P. Spatiotemporal modelling of CheY complexes in *Escherichia coli* chemotaxis. *Prog. Biophys. Mol. Biol.*, E-print PMID: 19540260, 2009.

Tindall, M.J., Maini, P.K., Armitage, J.P., Singleton, C. and Mason, A. Intracellular signalling during bacterial chemotaxis in *Practical Systems Biology* (Taylor and Francis), 61, 161-174, 2008.

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Tindall, M.J., Maini, P.K., Porter, S.L. and Armitage, J.P. Overview of mathematical approaches used to model bacterial chemotaxis II: Bacterial populations. *Bull. Math. Biol.*, 70(6), 1570-607, 2008.