

Modelling approaches in biology

Jean-Marc Schwartz

Faculty of Life Sciences
University of Manchester

jean-marc.schwartz@manchester.ac.uk

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CellDesigner

- CellDesigner is a modelling tool for systems biology. It contains a structured diagram editor for drawing gene-regulatory and biochemical networks.
- Networks are represented according to the Systems Biology Graphical Notation (SBGN).
- Models can be exchanged with other software using the Systems Biology Markup Language (SBML).
- CellDesigner is integrated with solvers for systems of ordinary differential equations (ODE), which enable it to run dynamic simulations and parameter scans.
- CellDesigner also supports referencing to external databases for the exchange of data and models.
- The software is freely available from <http://celldesigner.org/>

CellDesigner

The screenshot shows the CellDesigner 4.4 application window. The top menu bar includes: Apple logo, CellDesigner4.4, File, Edit, Component, View, Database, Layout, Simulation, Plugin, Window, SBW, Preference, Help, battery icon (39%), date (18 nov.), time (15:41), search icon, and a three-dot menu. Below the menu is a toolbar with numerous icons for file operations, selection, and modeling. To the left is a vertical sidebar with two expandable sections: 'Model' containing 'Compartments', 'Species', and 'Reactions'; and 'Layer' containing 'base'. The main workspace is currently empty. At the bottom, there is a tabbed panel with 'Species' selected, followed by 'Proteins', 'Genes', 'RNAs', 'asRNAs', 'Reactions', 'Compartments', 'Parameters', and 'Functions'. Below this panel is a table with columns: class, id, name, speciesType, compar..., positio..., included, quantit..., initialQuantity, sub..., hasO..., b.c., co... . There are also 'Edit' and 'Export' buttons. To the right of the table is a 'NOTE' section with a 'Edit Notes' button and a large empty text area.

Model

- Compartments
- Species
- Reactions

Layer

- base

Species Proteins Genes RNAs asRNAs Reactions Compartments Parameters Functions ►

Edit Export

class	id	name	speciesType	compar...	positio...	included	quantit...	initialQuantity	sub...	hasO...	b.c.	co...

NOTE MIRIAM

Edit Notes

CellDesigner

- Creating a new model:
 - Select File -> New in the menu. The New Document dialog appears.
 - Specify the name and size of the model, then click OK.
 - A white area appears in the Draw Area, where the model can be assembled.

CellDesigner

- Adding species to a model:
 - A **Species** in CellDesigner represents a type of molecule; for example a protein, DNA, metabolite, etc.
 - A **SpeciesAlias** is a graphical representation of a given Species. The same Species can have more than one associated SpeciesAlias.
 - To add a species to a model, select the appropriate type of molecule from the toolbar and click on the position where you want to place it in the Draw Area. The SpeciesAlias can be moved at will after being placed.
 - CellDesigner uses different symbols to distinguish between different types of molecules.

CellDesigner

Model

- Compartments
- Species
- Reactions

Layer

- base

TestModel *

Compound 1

Protein 1

Grid Snap OFF

Species Proteins Genes RNAs asRNAs Reactions Compartments Parameters Functions ►

Edit Export

class	id	name	speciesType	compar...	positio...	included	quantit...	initialQuantity	sub...	hasO...	b.c.	co...
PROTEIN	s1	Protein 1		default	inside		Amount	0.0		false	false	false
ION	s2	Compound 1		default	inside		Amount	0.0		false	false	false

NOTE MIRIAM

Edit Notes

CellDesigner

- To edit species properties, right-click on a SpeciesAlias and select Edit Species.
- Different protein residues can be associated to a protein: right-click on the target protein, then select Edit Protein. Click the Add button and fill in the information in the dialog that appears.
- You can view a list of all species belonging to your model in the Species list in the List Area.

CellDesigner

- Adding reactions to a model:
 - Select the appropriate type of reaction from the toolbar.
 - Click a starting SpeciesAlias.
 - Click an ending SpeciesAlias; the reaction link will be added.
- You can view a list of all reactions belonging to your model in the Reactions list in the List Area.

CellDesigner4.4 File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help 38% 18 nov. 15:47

CellDesigner

Model Compartments Species Reactions

Layer base

TestModel *

Compound rel1

Protein 1

Grid Snap OFF

Species Proteins Genes RNAs asRNAs Reactions Compartments Parameters Functions ►

Species ID Edit Export

type	id	name	reve...	fast	reactants	products	modifiers	math
STATE_TRANSITION	rel1		false	false	s2	s1		

NOTE MIRIAM

Edit Notes

CellDesigner

- Setting kinetic laws and parameters:
 - Right-click on the target reaction, then select Edit KineticLaw. The KineticLaw dialog will appear (Figure 4).
 - Enter the mathematical formula of the kinetic law in the Math textbox. Species IDs, not names, should be used in the formula. You can select the target species in the draw area and click the Copy button to insert its ID automatically.
 - To set a new **local parameter**, i.e. a parameter associated to a single reaction, select the Parameters tab at the bottom of the KineticLaw dialog, then click the New button and enter the data.

KineticLaw

math

Math
 Name

V SelectedReaction

s2
Compound  rel1 s1
Protein 1

V Predefined Functions

NonPredefinedFunction
Mass_Action_Kinetics
Irreversible_Simple_Michaelis-Menten

$v = k \prod_i S_i$

Species Parameters Rules

class	id	name	speciesType	compar...	positio...	included	quantit...
PROTEIN	s1	Protein 1		default	inside		Amount
ION	s2	Compound 1		default	inside		Amount

Update Cancel

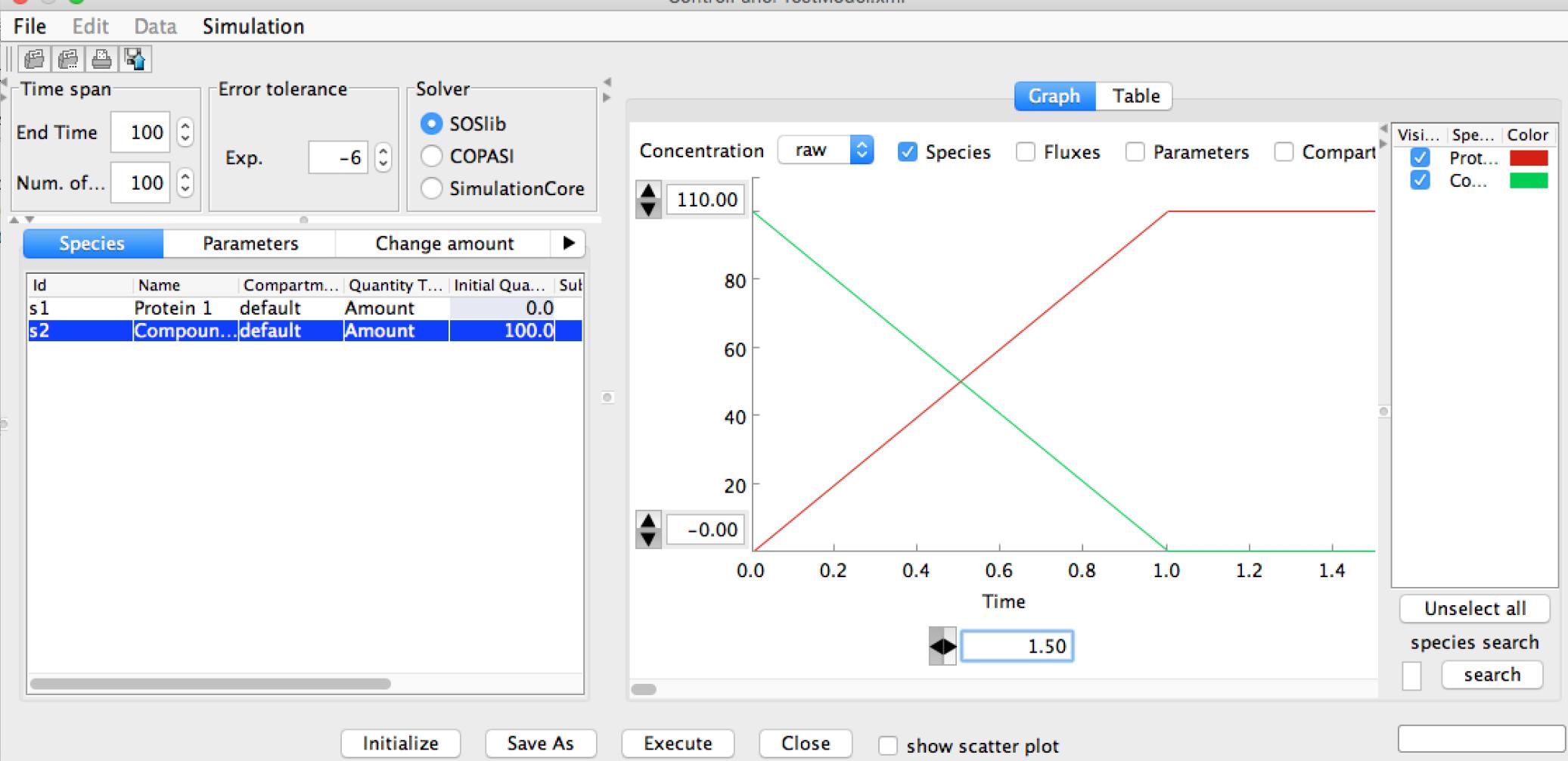
CellDesigner

- It is also possible to define [global parameters](#) in CellDesigner. A global parameter can be involved in several reactions of the model and must be defined from the Parameters tab in the list area.
- It is advisable to keep names of local and global parameters clearly distinct in order to avoid confusion.

CellDesigner

- Running simulations:
 - In the Menu, select Simulation -> ControlPanel. The control panel will open.
 - Enter the end time of the simulation and the number of values to be calculated. For example, if the end time is 1000 and the number of values is 100, then values will be calculated every 10 time units.
 - Click the Execute button.
 - A time course plot showing all species appears on the right side of the control panel. Axes scales may need to be adjusted and some species deselected if the model contains a large number of species.

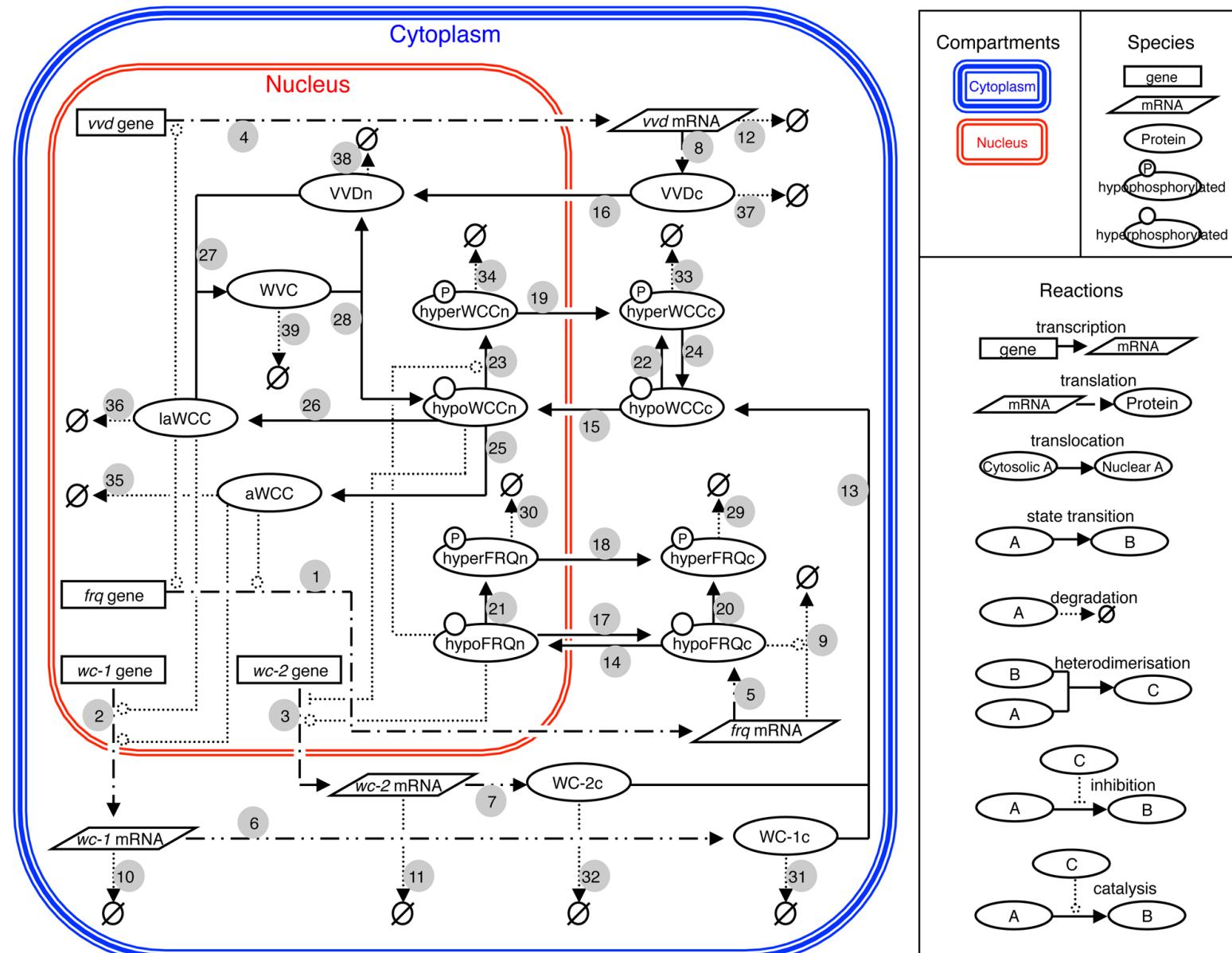
ControlPanel TestModel.xml



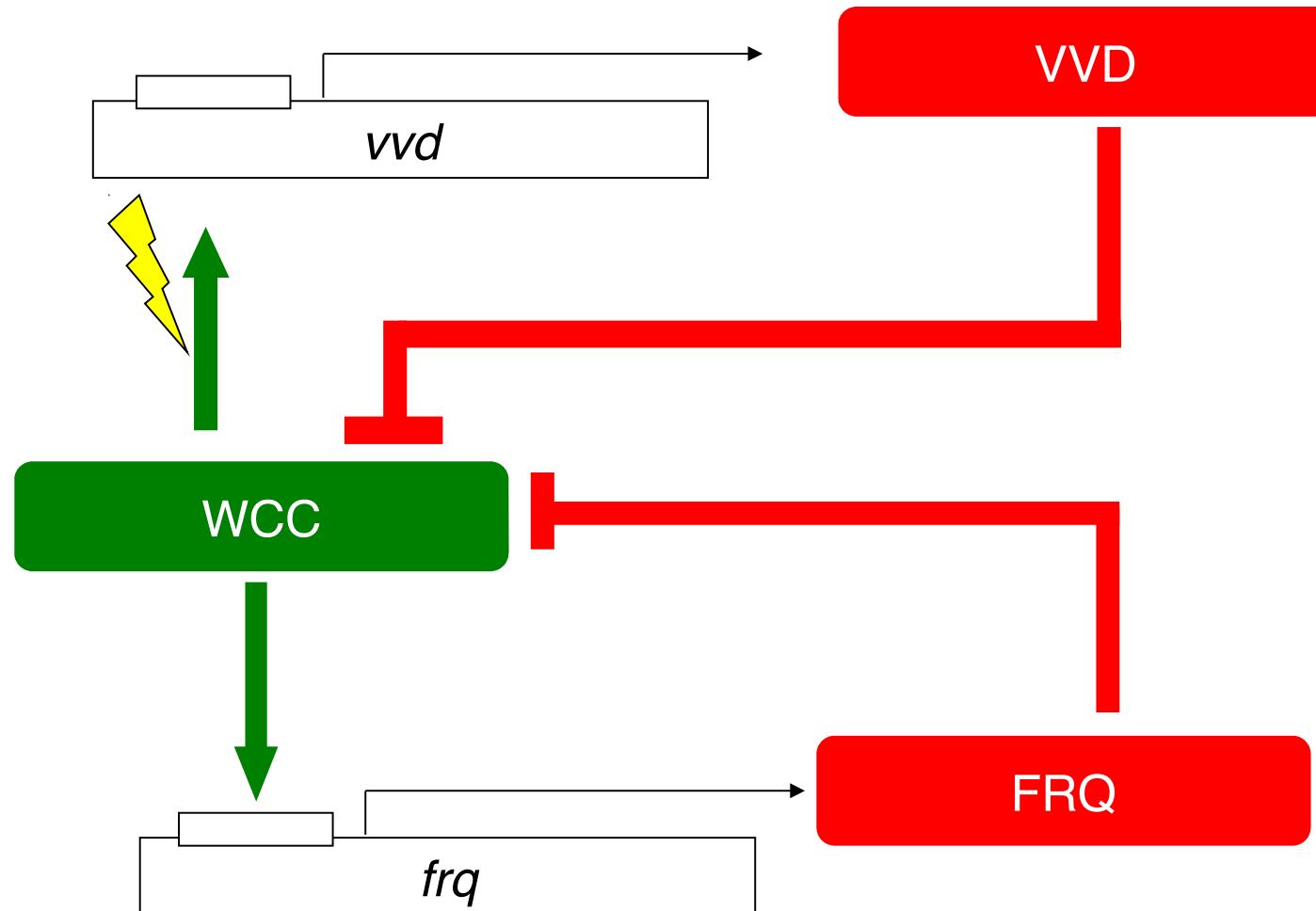
CellDesigner

- The solver can be changed to COPASI by selecting the corresponding radio button.
- The graph can be converted to a scatter plot: select any two species and tick the Show Scatter Plot checkbox.
- A table of simulated values can be obtained by selecting the Table tab.
- Both graph and table can be exported by clicking the Save As button.

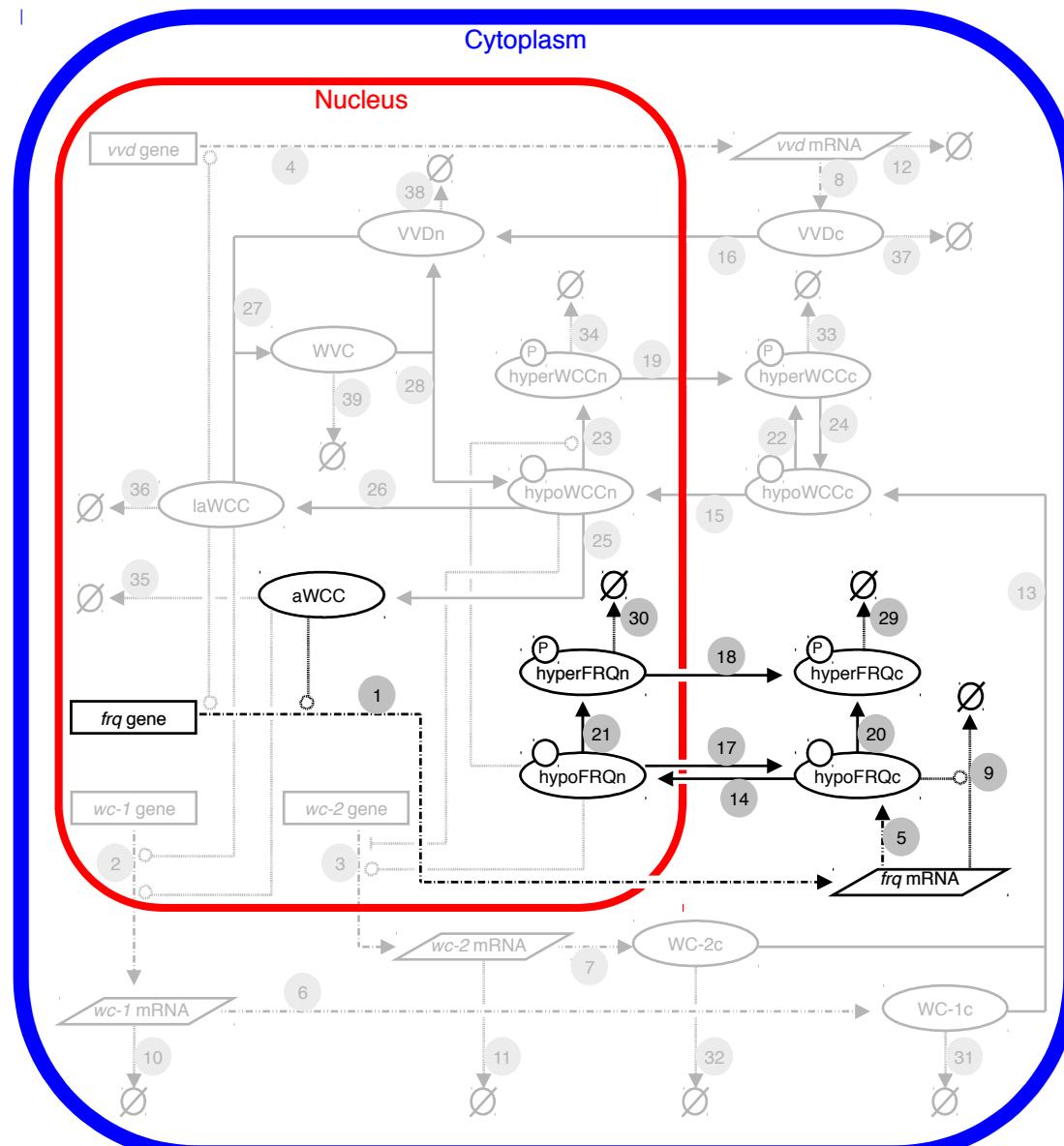
Example: Circadian clock of *Neurospora*



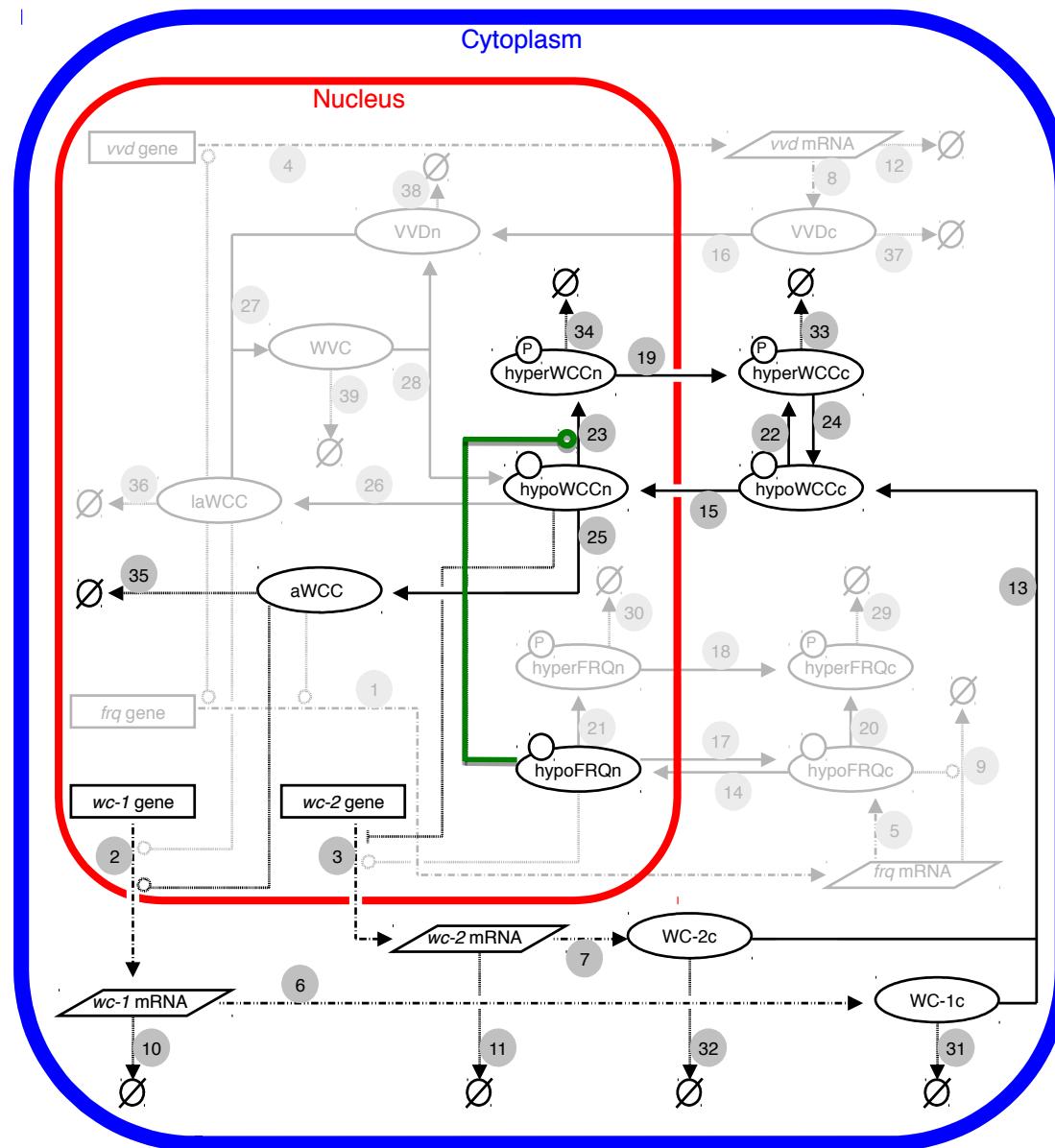
Example: Circadian clock of *Neurospora*



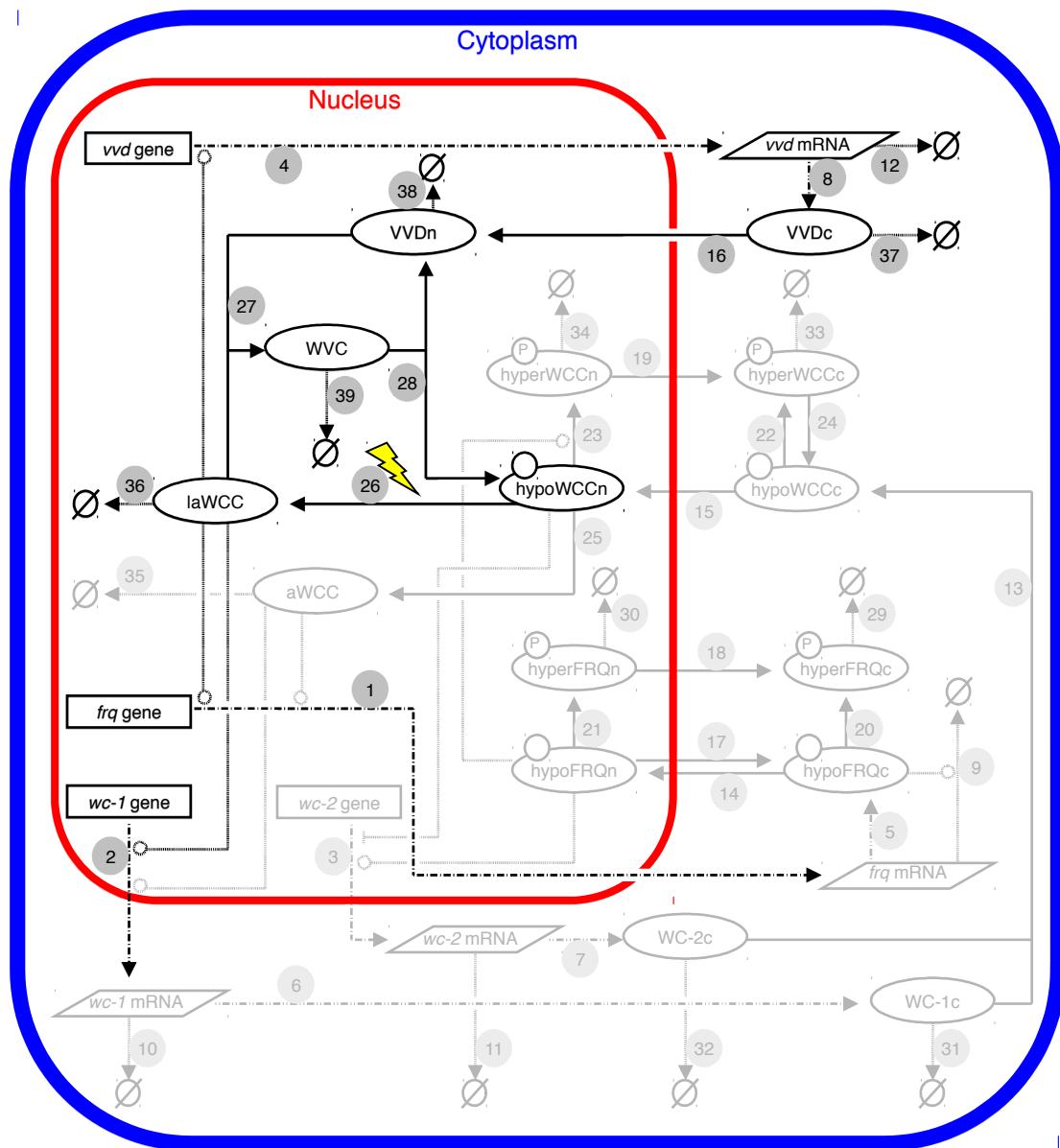
The expression of the central clock gene *frequency* is dependent on the transcription factor White Collar Complex (WCC).



The transcription factor WCC is composed of WC-1 and WC-2.
 WCC is inactivated by FRQ-dependent phosphorylation and
 degraded after initiation of transcription.



The transcription factor WCC can be activated by light and promotes the expression of light-induced genes.



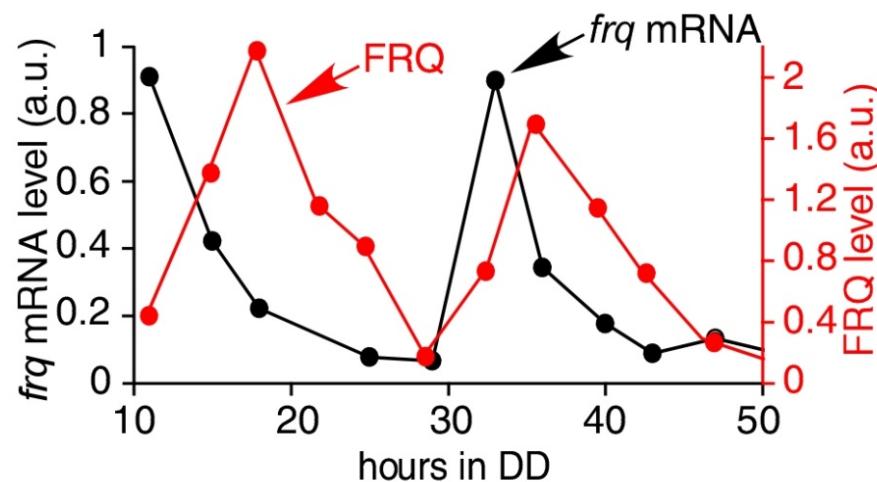
Light reactions reproduced in the model:

- (1) resetting by brief light pulses
- (2) entrainment to full photoperiods
- (3) photoadaptation

Clock characteristics

Experimental data

Garceau et al., 1997

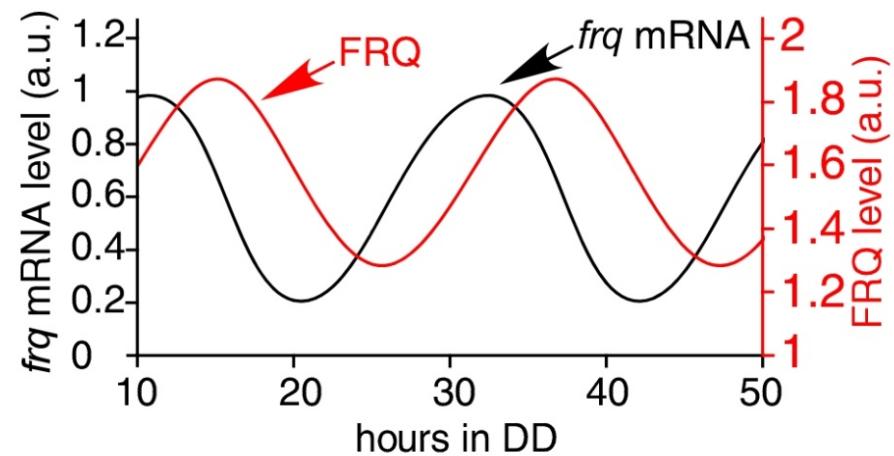


Period

22 hours

Model simulation

10 points per hour



21.6 hours

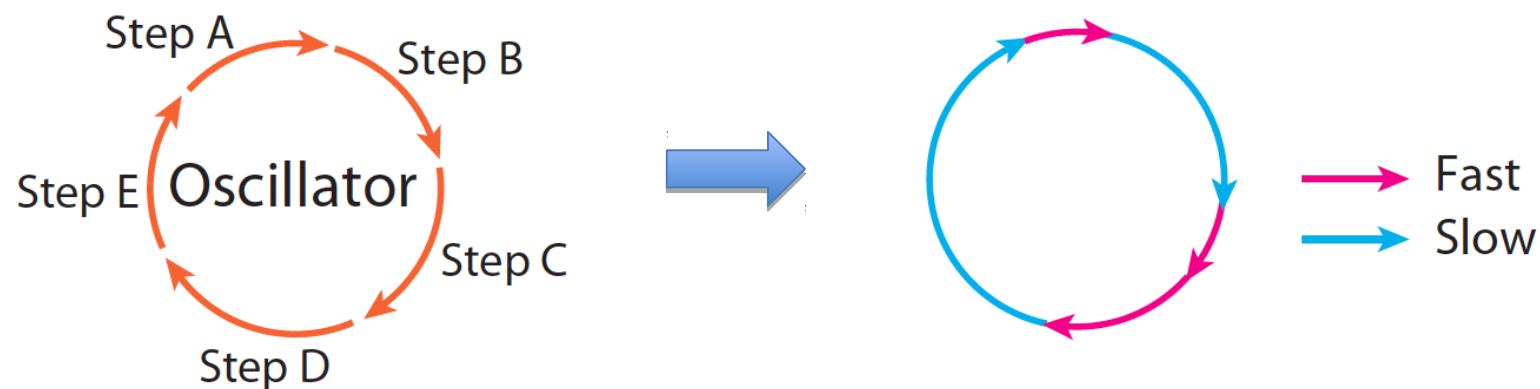
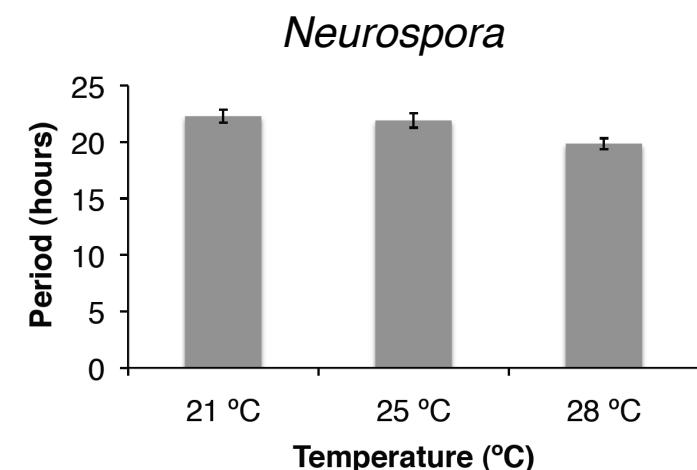
Time between peak
levels of *frq* mRNA
and FRQ protein

3-7 hours

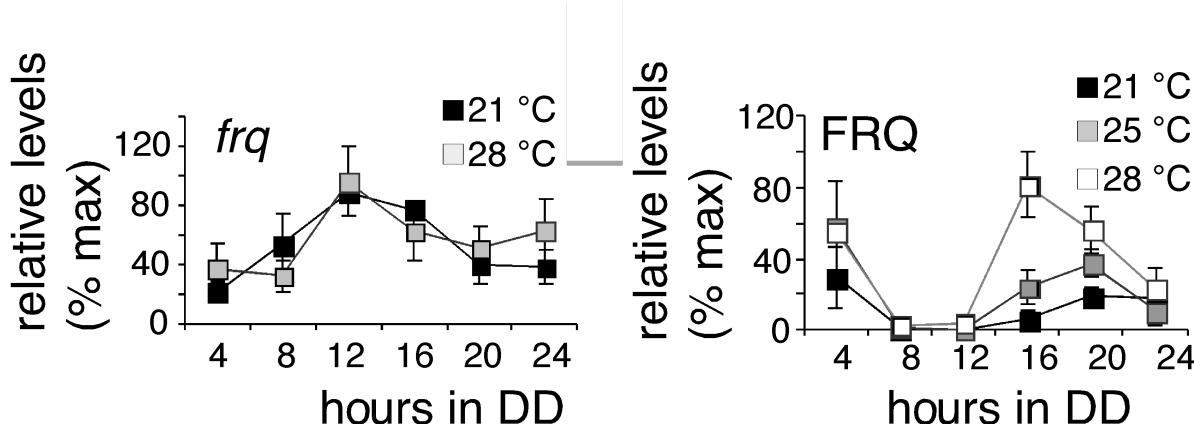
4.4 hours

Temperature compensation

- Temperature compensation allows organisms to maintain a constant period length in a range of temperatures.
- It is an important aspect of all circadian clocks and is especially important in organisms that cannot maintain their core body temperature.
- Temperature compensation can be achieved with balancing positive and negative contributions.



Temperature compensation



- The levels of *frq* mRNA and FRQ protein were measured at 21 °C and 28 °C by Northern and Western blotting analysis.
- The level of *frq* mRNA oscillation is constant at 21 and 28 °C.
- The level of FRQ oscillation is significantly increased from 21 to 28 °C.
- Mehra *et al.* (2009) showed that the degradation of FRQ is similar at 21 and 28 °C.
- Therefore *frq* translation increases as temperature increases.

Modelling temperature compensation

The effect of temperature was introduced into the model by use of the Arrhenius equation:

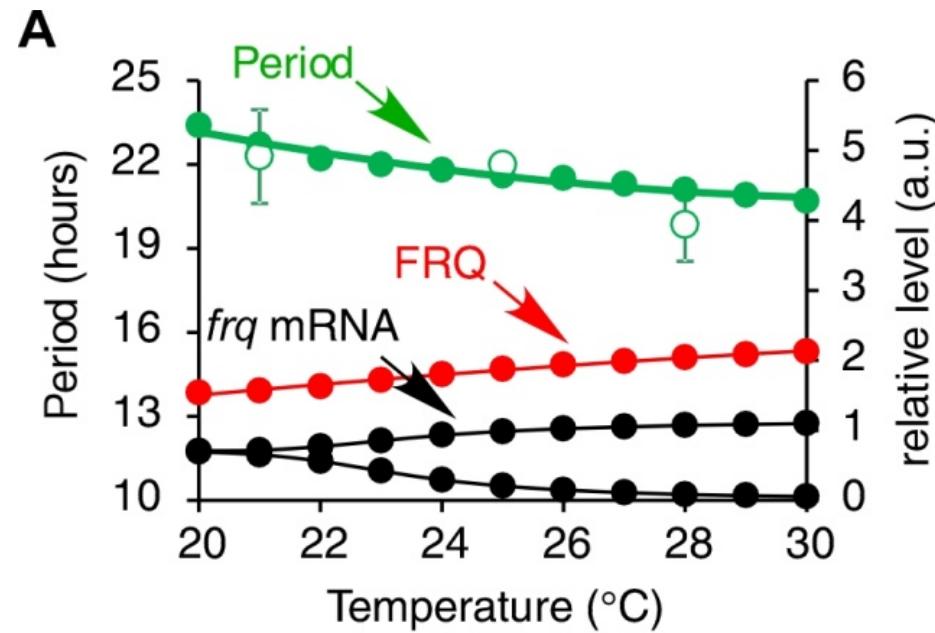
$$k_i = A_i e^{\frac{-E_i}{RT}}$$

Diagram illustrating the components of the Arrhenius equation:

- Kinetic parameter for temperature sensitive reaction i (blue arrow pointing to A_i)
- Activation energy (green arrow pointing to $-E_i$)
- Temperature in Kelvin (red arrow pointing to T)
- Gas constant (black arrow pointing to R)
- Pre-exponential factor (Arrhenius constant) (black arrow pointing to A_i)

Modelling temperature compensation

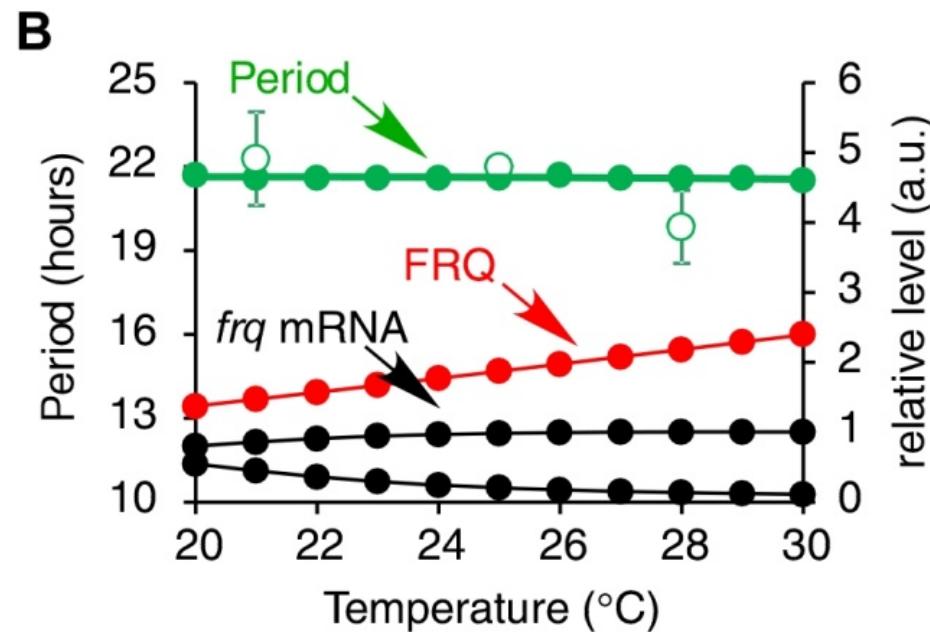
Hypothesis 1: *frq* translation increases as temperature increases.



- (1) Period decreases at higher temperature.
- (2) FRQ level does not triple from 21 °C to 28 °C.
- (3) *frq* RNA level decreases (data not shown).

Modelling temperature compensation

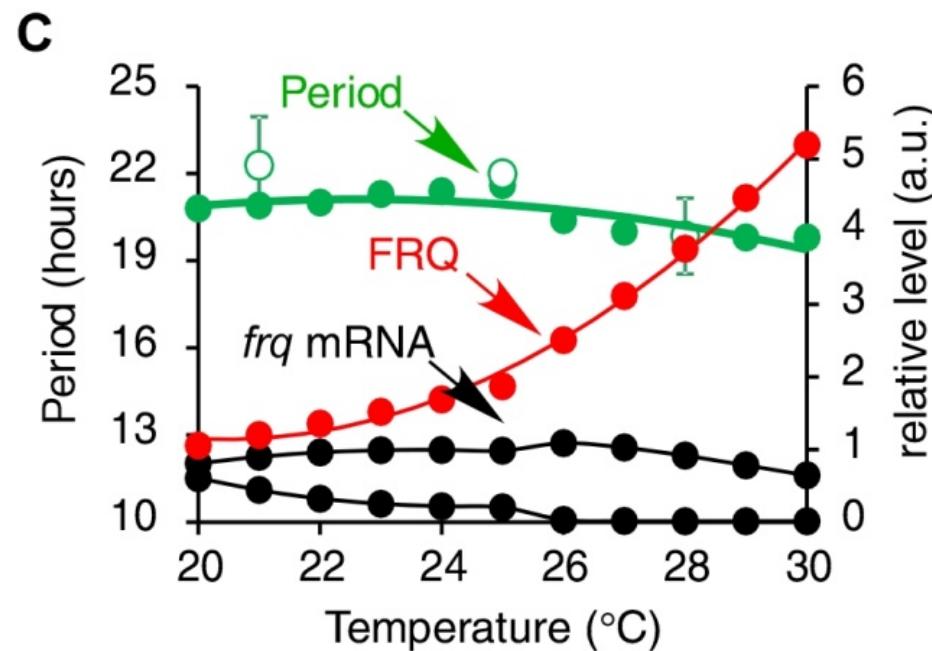
Hypothesis 2: *frq* translation increases and FRQ nuclear localisation decreases as temperature increases.



Period is constant, but FRQ level is not tripled from 21 °C to 28 °C.

Modelling temperature compensation

Hypothesis 3: *frq* translation increases and FRQ nuclear localisation decreases as temperature increases. *frq* translation has two different activation energies above and below 25 °C.



Period is nearly constant and FRQ level is tripled from 21 °C to 28 °C.

