Control eng in everyday’s life – cont’d
Problem Statement and main goal
“Biological circuitry”
Gene activation and repression

\[
\frac{d B}{d t} = \alpha + \beta \frac{A^h}{K^h + A^h} - d
\]

\[
\frac{d B}{d t} = \alpha + \beta \frac{1}{1 + \left(\frac{A}{K}\right)^h} - d
\]
"Biological circuitry": modelling

\[
\begin{align*}
\frac{dX_{\text{mRNA}}}{dt} &= k_1 + k_2 f_1(X_{\text{protein}}) - d_1 X_{\text{mRNA}} \\
\frac{dX_{\text{protein}}}{dt} &= k_3 X_{\text{mRNA}} - d_2 X_{\text{protein}} \\
\frac{dY_{\text{mRNA}}}{dt} &= k_4 + k_5 f_2(Y_{\text{protein}}, X_{\text{protein}}; \text{met}) - d_3 Y_{\text{mRNA}} \\
\frac{dY_{\text{protein}}}{dt} &= k_6 Y_{\text{mRNA}} - d_4 Y_{\text{protein}} \\
\frac{dm_{\text{met}}}{dt} &= 0
\end{align*}
\]
Controlling a biological system

Protein B (oncosuppressor)

Protein A (oncogene)
“What I cannot create I do not understand!”

R. Feynman
Cellular regulation by molecular network postulated by Jacob and Monod.

Development of molecular cloning techniques.

Rise of ‘omics’ and high-throughput biology.

Widespread DNA sequencing and gene expression chips.

Synthetic circuits to study transcriptional noise.

First "edge detector" and "counter" circuits devised.

CRISPR-CAS9 genome editing system.

First Synthetic organisms by JCVI...


2002 Synthetic circuits to study transcriptional noise.

2009 First "edge detector" and "counter" circuits devised.

2011 First Synthetic organisms by JCVI...

2012 CRISPR-CAS9 genome editing system.

2000 Widespread DNA sequencing and gene expression chips.

1990s Development of molecular cloning techniques.


1970s Development of molecular cloning techniques.

1960s Cellular regulation by molecular network postulated by Jacob and Monod.

readapted from (Cameron et al, 2014)
A synthetic oscillator: the repressilator

\[
\frac{dm_1}{dt} = \quad \frac{dm_2}{dt} = \quad \frac{dm_3}{dt} =
\]
Model Systems: GAL1 vs IRMA

GAL1 System

\[ G(s) = \mu \frac{e^{-ds}}{1 + \Theta_s} \]

IRMA

\[
\frac{dx_1}{dt} = \alpha_1 + v_1 \left( \frac{x_{3}^{h1}(t-\tau)}{(k_{3}^{h1} + x_{3}^{h1}(t-\tau)) \cdot \left(1 + \frac{x_2^{h2}}{k_2^{h2}}\right)} \right) - d_1 x_1
\]

\[
\frac{dx_2}{dt} = \alpha_2 + v_2 \left( \frac{x_1^{h2}}{k_1^{h2} + x_1^{h2}} \right) - d_2 x_2
\]

\[
\frac{dx_3}{dt} = \alpha_3 + v_3 \left( \frac{x_2^{h3}}{k_2^{h3} + x_2^{h3}} \right) - d_3 x_3
\]

\[
\frac{dx_4}{dt} = \alpha_4 + v_4 \left( \frac{x_3^{h4}}{k_3^{h4} + x_3^{h4}} \right) - d_4 x_4
\]

\[
\frac{dx_5}{dt} = \alpha_5 + v_5 \left( \frac{x_3^{h5}}{k_5^{h5} + x_3^{h5}} \right) - d_5 x_5
\]
Model Systems: GAL1 vs IRMA

GAL1 System

\[ G(s) = \mu \frac{e^{-ds}}{1 + \Theta s} \]

IRMA
Control algorithm design

\[ y_{\text{ref}} \xrightarrow{+} e \xrightarrow{-} \hat{u} \xrightarrow{\text{PWM}} u \xrightarrow{\text{Pred}} y \]

Pred

\[ u \xrightarrow{\text{M}} \hat{y} \xrightarrow{e^{-\tau s}} \hat{y}_\tau \xrightarrow{-} \xrightarrow{\text{F}} y_s \]
In-silico test
Microfluidics

(Odijk et al., 2009)

(Bennet and Hasty, 2009)

(Bennet and Hasty, 2009)

(Elveflow.com)
Microfluidic device
Microfluidic device fabrication
Microfluidic device: operations

MFD0005_d

D  Loading

E  Running
Microfluidic device: fluid dynamics
Microfluidic device: input modulation

A

$\Delta H = 0$
$R = 50\%$

B

$\Delta H = 50$
$R = 75\%$

C

$\Delta H = 100$
$R = 100\%$

D

$\Delta H = 150$
$R = 125\%$

1 1 1 1

0.5 0.5 0.75 0.25 1 1 1 1

1.5 1.5 1.75 1.25 2 1 2.25 0.75 1 1 1 1
Microfluidic device: input modulation
Microfluidic actuation

(Ferry et al, 2011)
Real-time input control
Hydrostatic actuation
Microfluidic device: input modulation
Control loop
Signal extraction: image processing

- Bright field
- Bright field mask
- Masked fluorescent field
Signal extraction: image processing

GFP signal

GFP background
Preliminary experiments: Gal step

INPUT

Glu

Gal

OUTPUT

Glu

Gal

Glu

Glu

Graph showing time (min) vs. a.u. with data points and lines indicating input and output changes over time.
Preliminary experiments: Gal 3 hrs sq

INPUT

Gal
Glu

OUTPUT

Glu
Gal

Graph showing time (hrs) vs. signal intensity.
In-vivo setpoint control GAL1

A

B

C

D

THE UNIVERSITY of EDINBURGH
In-vivo signal tracking control IRMA
Results – Control of IRMA
Results – Control of IRMA
Control of mammalian cells

CHO tet–OFF cells

\[
\frac{dx_1}{dt} = v_1 \left( \alpha_1 + (1 - \alpha_1) \frac{\left( \frac{\theta^{h_2}}{\theta^{h_2} + D^{h_2} \bar{x}_2} \right)^{h_1}}{K_1^{h_1} + \left( \frac{\theta^{h_2}}{\theta^{h_2} + D^{h_2} \bar{x}_2} \right)^{h_1}} \right) - d_1 x_1,
\]

\[
\frac{dx_3}{dt} = v_2 x_1 - (d_3 + K_f) x_3,
\]

\[
\frac{dx_4}{dt} = K_f x_3 - d_3 x_4.
\]

d2EYFP mRNA

d2EYFP unfolded protein

d2EYFP folded protein
Results: setpoint control of CHO cells

(Fracassi et al, 2015)
Viability of CHO cells in mFluidics

Chinese Hamster Ovary (CHO) cells on uncoated glass
experiment duration: 5 days

An algorithm computes a mask on the phase contrast image

Quantification of fluorescence is reliable only with non-confluent cells

(Fracassi et al, 2015)
Future directions for Systems and Synthetic Biology
Designing better experiments: OED

argmax F(u)

(Optimal Experiment Designer)
Optimal input design in microfluidics
Better parametric estimates
Applications: Rapid Prototyping

Model matching → Specs

Characterize circuit → Design DNA → Transform cells

DNA matching → Transform cells

Questions mark
Applications: Cancer fighting bacteria
Control loop
Feedback control for combination therapy
\[
\begin{align*}
\frac{dx_1}{dt} &= \alpha_1 + v_1 \left( \frac{x_{31}^{h_1}(t - \tau)}{(x_{h_1} + x_{31}^{h_1}(t - \tau)) \cdot \left(1 + \frac{x_{32}^{h_2}}{k_{h_2}}\right)} \right) \\
&\quad - d_1 x_1 \\
\frac{dx_2}{dt} &= \alpha_2 + v_2 \left( \frac{x_{31}^{h_2}}{k_{h_2} + x_{31}^{h_2}} \right) - d_2 x_2 \\
\frac{dx_3}{dt} &= \alpha_3 + \bar{v}_3 \left( \frac{x_{h_3}^{h_3}}{k_{h_3} + x_{h_3}^{h_3}(1 + \frac{x_{h_1}^{h_1}}{k_{h_1}})} \right) - d_3 x_3 \\
\frac{dx_4}{dt} &= \alpha_4 + v_4 \left( \frac{x_{h_3}^{h_3}}{k_{h_3} + x_{h_3}^{h_3}} \right) - d_4 x_4 \\
\frac{dx_5}{dt} &= \alpha_5 + v_5 \left( \frac{x_{h_3}^{h_3}}{k_{h_3} + x_{h_3}^{h_3}} \right) - d_5 x_5
\end{align*}
\]
Results – Control of IRMA

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(Menolascina et al, 2014)

(Menolascina et al, 2010)
Thanks!