These transparencies were presented at the Computation in Cells workshop on Tuesday April 18, 2000 in Hertfordshire, UK and partially at the tutorial on Saturday April 15, 2000 at the Euro-GP-2000 conference in Edinburgh.
REVERSE ENGINEERING OF METABOLIC PATHWAYS

COMPUTATION IN CELLS
UNIVERSITY OF HERTFORDSHIRE
HATFIELD CAMPUS
TUESDAY — APRIL 18, 2000

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REVERSE ENGINEERING OF METABOLIC PATHWAYS

4-REACTION NETWORK IN PHOSPHOLIPID CYCLE
## 9 FITNESS CASES

<table>
<thead>
<tr>
<th>Fitness Case</th>
<th>EC2.7.1.30</th>
<th>EC3.1.3.21</th>
<th>EC3.1.1.23</th>
<th>EC3.1.1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slope-Up</td>
<td>Saw</td>
<td>Step-Down</td>
<td>Step-Up</td>
</tr>
<tr>
<td>2</td>
<td>Slope-Down</td>
<td>Step-Up</td>
<td>Saw</td>
<td>Step-Down</td>
</tr>
<tr>
<td>3</td>
<td>Step-Down</td>
<td>Slope-Up</td>
<td>Step-Down</td>
<td>Step-Up</td>
</tr>
<tr>
<td>4</td>
<td>Step-Up</td>
<td>Slope-Down</td>
<td>Step-Up</td>
<td>Step-Down</td>
</tr>
<tr>
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<td>Saw</td>
<td>Step-Down</td>
<td>Slope-Up</td>
<td>Step-Up</td>
</tr>
<tr>
<td>6</td>
<td>Saw</td>
<td>Knock-Out</td>
<td>Step-Down</td>
<td>Slope-Up</td>
</tr>
<tr>
<td>7</td>
<td>Saw</td>
<td>Knock-Out</td>
<td>Step-Down</td>
<td>Step-Down</td>
</tr>
<tr>
<td>8</td>
<td>Knock-Out</td>
<td>Step-Down</td>
<td>Slope-Up</td>
<td>Saw</td>
</tr>
<tr>
<td>9</td>
<td>Step-Down</td>
<td>Slope-Up</td>
<td>Saw</td>
<td>Knock-Out</td>
</tr>
</tbody>
</table>

### SLOPE-UP

![Graph showing concentration over time for SLOPE-UP](image1)

### SLOPE-DOWN

![Graph showing concentration over time for SLOPE-DOWN](image2)
KNOCK-OUT

![Graph showing Concentration over Time](image)
CONCENTRATIONS OF PROBED PRODUCT C00165 - DIACYL-GLYCEROL FOR 9 FITNESS CASES

FIRST 15 SECONDS OF C00165

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration of C00165</th>
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</thead>
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<tr>
<td>1</td>
<td>0.1221372</td>
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<tr>
<td>2</td>
<td>0.2168507</td>
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<td>3</td>
<td>0.280057</td>
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<tr>
<td>11</td>
<td>0.44706</td>
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<td>12</td>
<td>0.4541539</td>
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<tr>
<td>13</td>
<td>0.4676479</td>
</tr>
<tr>
<td>14</td>
<td>0.4810823</td>
</tr>
</tbody>
</table>
FITNESS

• We vary the concentration of specified substance(s), such as substrates (inputs) or catalysts (enzymes), over time
  • In the example, the concentration of 4 enzymes is varied
  • In the example, 9 different scenarios (fitness cases)
  • In the example, each scenario is simulated for 30 seconds

• We probe (as output) the concentration of specified product substance(s) produced by the network of reactions.
  • In the example, C00165 - Diacyl-glycerol is probed

• Each actual network of reactions is exposed to the 9 30-second input scenarios (the fitness cases) and the actual concentration of the probed product substance(s) are recorded.

• Each individual network of reactions at each generation of the population is, at each generation, exposed to the same 9 30-second input scenarios (the fitness cases) and the concentration of the probed product substance(s) are recorded (for comparison).

• The fitness of an individual reaction network is the sum of the absolute weighted differences (errors)
  • The weight is 1 if the error is within 5%
  • The weight is 10 if the error is greater than 5%
**BEST-OF-GENERATION 0**

- **EC3.1.1.23** (K = 1.10 (1.95))
  - Acylglycerol lipase
  - C00116
  - Glycerol
- **EC3.1.1.3** (K = 1.47 (1.45))
  - Triacylglycerol lipase
  - Int
- **C00162**
  - Fatty Acid
- **C00116**
  - Glycerol
- **C00002**
  - ATP
- **C00165**
  - Diacyl-glycerol

**BEST-OF-GENERATION 9**

- **EC3.1.1.23** (K = 1.90 (1.95))
  - Acylglycerol lipase
  - C00116
  - Glycerol
- **EC3.1.3.21** (K = 0.78 (1.19))
  - Glycerol-1-phosphatase
  - Int
- **EC2.7.1.30** (K = 1.81 (1.69))
  - Glycerol kinase
- **C00116**
  - Glycerol
- **C00002**
  - ATP
- **C00165**
  - Diacyl-glycerol
- **C00162**
  - Fatty Acid

Cell Membrane
**BEST-OF-GENERATION 17**

- **EC3.1.1.23**
  - $K = 0.79 (1.95)$
  - Acylglycerol lipase
  - C00162
  - Glycerol
  - Int

- **EC3.1.1.3**
  - $K = 1.00 (1.45)$
  - Triacylglycerol lipase
  - C00165
  - Diacyl-glycerol

- **EC3.1.3.21**
  - $K = 0.65 (1.19)$
  - Glycerol-1-phosphatase
  - C00116
  - Glycerol

- **EC2.7.1.30**
  - $K = 1.81 (1.69)$
  - Glycerol kinase
  - C00002

- **BEST-OF-GENERATION 19**

- **EC3.1.1.23**
  - $K = 1.41 (1.95)$
  - Acylglycerol lipase
  - C00162
  - Glycerol
  - Int

- **EC3.1.1.3**
  - $K = 1.60 (1.45)$
  - Triacylglycerol lipase
  - C00165
  - Diacyl-glycerol

- **EC3.1.3.21**
  - $K = 1.56 (1.19)$
  - Glycerol-1-phosphatase
  - C00116
  - Glycerol

- **EC2.7.1.30**
  - $K = 1.65 (1.69)$
  - Glycerol kinase
  - C00002

- **Cell Membrane**

**OUTPUT (MEASURED)**
**BEST-OF-GENERATION 66**

**EC3.1.1.23**  
*K* = 1.88 (1.95)  
Acylglycerol lipase  
Output (measured)

**EC3.1.1.3**  
*K* = 1.46 (1.45)  
Triacylglycerol lipase

**EC3.1.3.21**  
*K* = 1.20 (1.19)  
Glycerol-1-phosphatase

**EC2.7.1.30**  
*K* = 1.65 (1.69)  
Glycerol kinase

**EC3.1.1.3**  
*K* = 1.95

**EC3.1.3.21**  
*K* = 1.19

**EC2.7.1.30**  
*K* = 1.69

**DESIRE**

**EC3.1.1.23**  
*K* = 1.95  
Acylglycerol lipase

**EC3.1.1.3**  
*K* = 1.45  
Triacylglycerol lipase

**EC3.1.3.21**  
*K* = 1.19  
Glycerol-1-phosphatase

**EC2.7.1.30**  
*K* = 1.69  
Glycerol kinase

**EC3.1.1.3**  
*K* = 1.95

**EC3.1.3.21**  
*K* = 1.19

**EC2.7.1.30**  
*K* = 1.69

**OUTPUT (MEASURED)**

**OUTPUT (MEASURED)**